REMARKS

Claims 1-20 remain in this application. Applicant submits that this Response places this application in condition for allowance by providing remarks and supplemental data that are believed to render all pending claims allowable over the cited art and/or at least place this application in better form for appeal. Accordingly, entry of the present Response, as an earnest attempt to advance prosecution and/or to reduce the number of issues, is requested under 37 C.F.R. §1.116.

CLAIM REJECTION - 35 USC § 103

At page 3, the Office Action rejects claims 1-20 under 35 U.S.C. § 103(a) as being unpatentable over AGERUP (US 5,827,937) in view of MILLER (US 6,174,999). Applicants respectfully traverse the rejection.

DISTINCTION OVER AGERUP AND MILLER

Present claim 1 is directed to a process for the production of a biocompatible crosslinked gel. The process features in part: starting a crosslinking reaction of a predetermined quantity of at least one biocompatible polymer, crosslinking the polymer, and then adding a supplemental quantity of polymer (of a molecular weight higher than 500,000 Da) with dilution of the reaction mixture so as to decrease the overall concentration of the polymer in solution, and continuing

crosslinking. Finally, the process includes stopping the crosslinking reaction by elimination of the crosslinking agent. AGERUP fails to teach or suggest a process having this combination of steps.

AGERUP describes a process for the production of a biocompatible cross-linked gel that includes: starting a cross-linking reaction biocompatible polymer, sterically hindering the cross-linking reaction from being terminated before gelation occurs to obtain an activated polysaccharide, and reintroducing sterically unhindered conditions to the activated polysaccharide to continue the cross-linking to form the gel (see, Abstract). The presently claimed process is distinct from the AGERUP process and produces a gel that is different than that produced by AGERUP.

The AGERUP method involves cross-linking a polysaccharide in two stages, where the cross-linking is discontinued before the gelation is initiated (see, column 2, lines 62-67). The discontinuance before gelation produces an activated polysaccharide. Then, polymerization of the activated polysaccharide is continued to produce the gel (see, column 3, lines 3-7). The stopping and starting of the cross-linking reaction is the result of controlling the steric hindrance conditions. AGERUP discloses that its method produces a gel that has a less compact and less dense structure and results in a more visoelastic gel (see, column 3, lines 7-12). AGERUP theorizes

that the structure results from the combination of cross-linking between existing polymer chains and an elongation of existing chains (see, column 3, lines 17-22).

The presently claimed method has a series of steps that are different than AGERUP. This method starts a cross-linking reaction and cross-links a quantity of polymer. The claimed method does not hinder the cross-linking reaction, sterically or otherwise. Then, a supplemental quantity of polymer is added to the reaction which is accompanied by the dilution of the reaction medium such that the overall concentration of polymer is the solution decreases with continuing cross-linking.

As detailed in the specification, by adding the supplemental quantity of polymer the polymer chains have new cross-linking sites that react with the residual cross-linkage agent. Under these conditions, however, of decreasing the concentration of polymer and decreasing the quantity of cross-linking agent, the number of bridges on the chains of gel formed in the first step of cross-linking is greater than the number of bridges between the added chains in the second step. The degree of cross-linking thus varies in the final gel which is constituted by strongly cross-linked hubs (e.g. 25%) interconnected by a gel which is less and less cross-linked (progressively decreasing to about e.g. 1%). (See specification, page 10, line 23 to page 11, line 9).

In the present method, the addition of supplemental polymers takes place at any level of progress of the initial cross-linkage reaction, "preferably at 75% of the initial cross linkage reaction." (See, page 11, lines 15-17). Finally, the process as claimed obtains a biocompatible cross-linked gel having the characteristics of being monophasic, polydensified, cohesive, injectible and with long remainance (see, page 11, line 30 to page 12, line 2).

The Office Action appears to misinterpret the teachings of AGERUP and the sequence of steps used in the AGERUP process. The Office Action states that AGERUP discloses a process that includes "diluting the reaction mixture to decrease the concentration of polymer in solution" (see, page 4 of Office Action). AGERUP discloses that a preferred technique of "sterical hindrance" of the cross-linking reaction comprises diluting the aqueous medium to accomplish a lower-concentration of the polysaccharide (see, column 3, lines 41-47). This step is associated with "sterically hindering the cross-linking reaction from being terminated before gelation occurs to obtain an activated polysaccharide." Importantly, the AGERUP method follows this with reintroducing "sterically unhindered" conditions to the activated polysaccharide to continue the cross-linking to form the gel. This preferably occurs by evaporating or dialyzing the aqueous medium to accomplish a higher concentration of the polysaccharide (see, column 3, lines 48-56). AGERUP coins this

as the "dilution-concentration technique" (see, column 4, lines 53-54).

The presently claimed method includes adding a supplemental quantity of polymer (MW > 500KDa) with dilution of the reaction mixture and continuing cross-linking. First, in contrast to AGERUP, no "steric hindrance" occurs because the cross-linking continues, albeit at a progressively decreasing level of cross-linking. The Office Action recognizes that AGERUP next teaches sterically unhindered conditions of "supplementing the polymer concentration in solution and accelerating the rate of the crosslinking reaction" and "the step of increasing the polymer concentration and crosslinking reaction rate" (see, page 4 and page 5 of the Office Action). This lies in distinction from the presently claimed method which does not utilize the "dilution-concentration" process.

The Office Action also understands that AGERUP discloses that "sterically hindering" the cross-linking reaction means diluting the reaction mixture and lowering the concentration of polymer. Re-introducing "stearically unhindered" conditions means accomplishing a higher concentration of the polymer to enable a more rapid reaction to take place relative to the sterically hindered condition. (See, page 8 of the Office Action). As discussed in the above remarks, however, the presently claimed method does not follow this "dilution-concentration" series of steps.

The Office Action relies on MILLER merely for teaching how to stop a polymerization reaction by eliminating a non-polymeric reactant from the reaction mixture by dialysis. MILLER, however, fails to remedy the above noted deficiencies of AGERUP.

COMPARATIVE DATA

At pages 9-10, the Office Action allows that this rejection can be overcome by providing additional support in the form of comparative data that establishes factual evidence that the respective polymer gels produced by the presently claimed method and the AGERUP method produce patentably distinct products. Applicants submit herein such comparative data. Supporting documents are provided in the attached Appendix.

First, the AGERUP patent (US 5,287,937) has been assigned to a Swedish company Q Med AB. As shown in the attached "Annual Report" of Q Med for 1999, the product sold under the name RESTYLANE is prepared according to the method of the AGERUP '937 patent. See, page 11, column 1 "Patents and trademarks", page 13, column 2 "RESTYLANE" and particularly, pages 20-21 "Legal dispute with Biomatrix" (see, page 21, column 1, lines 1-4).

Also, as shown in the attached "Certificate Extending Patent Term Under 35 U.S.C. § 156" the AGERUP '937 patent was

granted an extension of term based upon FDA regulatory review of the product RESTYLANE.

Additionally, the document of VERPAELE et al. (Restylane SubQ, a Non-Animal Stabilized Hyaluronic Acid Gel for Soft Tissue Augmentation of the Mid- and Lower Face, *Aesthetic Surgery Journal* (2006)) also shows that the RESTYLANE product is manufactured according to the AGERUP patent and is described as a "biphasic" gel. Further information can be found on the Q Med website at www.q-med.com.

Thus, RESTYLANE corresponds to a polysaccharide gel produced by the method of AGERUP.

Second, in respect to a gel produced by the presently claimed method, a gel marketed by Anteis under the name ESTHELIS and marketed in Germany under the name BELOTERO by a licensee of Anteis is produced by the presently claimed method. Therefore, a biocompatible gel of the presently claimed method can be compared to that of AGERUP and such comparative data has been provided as detailed below.

VERPAELE et al. indicates that RESTYLANE is made of gel particles in what can be described as a "biphasic" gel (see, in particular, Figure 3). This is in distinction to the gel produced according to the present specification which is a "monophasic" gel (see, for example, page 4, lines 19-26, and page 6, lines 15-18).

BERGERET-GALLEY (Choosing Injectable Implants According to Treatment Area: The European Experience, *Facial Plastic Surgery* (2009)) explains in detail the difference between biphasic implants such as RESTYLANE and monophasic implants such as that produced by the presently claimed method (see, page 138).

REINMULLER (81% Success Rate in the Treatment of Nasolabial Folds, *Dermatology News* (2007)) illustrates a difference between biphasic and monophasic gels (see, Figures 4 and 5).

BEZZOLA et al. (Esthelis, hyaluronic acid of Swiss design, *J. Med. Esth. Et Chir. Derm.* (2005)) further states that RESTYLANE is biphasic and ESTHELIS is monophasic (see, page 12, column 1 and page 14, column 1).

Internal report of Anteis (Essais Bleu de Toluidine) provides coloration tests with toluidine blue which clearly show that a biphasic product such as RESTYLANE has a very different structure than a monophasic product such as ESTELIS. Staining of the biphasic product shows HA particle “chunks” compared to the “spider web” network of the monophasic product.

Extract from BELOTERO leaflet where histological tests show that the diffusion of the products, RESTYLANE and BELOTERO, are different in the derm, resulting in different tissue reactions. Also, the structure of the two gels are different.

GOLD (Soft Tissue Augmentation in Dermatology, *Journal of Cutaneous and Aesthetic Surgery* (2010)) describes the

structural differences between monophasic and biphasic gels. Monophasic gels are more cohesive, have better persistence and poor migration. Biphasic gels are less cohesive, lower persistence and visible migration. Each of the two types of gels have different advantages and inconveniences.

In summary, the attached documents establish that the AGERUP '537 describes a method that produces a "biphasic" gel product. In distinction, the presently claimed method produces a "monophasic" gel. The two gels are different in several aspects as detailed by the evidence provided in the attached documents. Thus, applicants have provided support and comparative data to establish that the respective polymer gels are distinct products.

For all of the reasons as set forth in the above remarks, AGERUP and MILLER fail to teach or suggest, and would not have rendered obvious, the method of claims 1-9 and 13-18, the gel of claims 10-11 and the method of claim 12. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

Entry of the above amendments is earnestly solicited. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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HJV/jr

APPENDIX:

The Appendix includes the following 9 documents:

- Annual Report of Q Med for 1999
- Certificate Extending Patent Term Under 35 U.S.C. § 156, AGERUP patent (US 5,287,937)
- Verpaele et al. "Restylane SubQ, a Non-Animal Stabilized Hyaluronic Acid Gel for Soft Tissue Augmentation of the Mid- and Lower Face", *Aesthetic Surgery Journal* (2006)
- Rapport Interne Anteis
- Bergeret-Galley, "Choosing Injectable Implants According to Treatment Area: The European Experience", *Facial Plastic Surgery* (2009)
- Reinmuller "81% Success Rate in the Treatment of Nasolabial Folds", *Dermatology News* (2007)
- Bezzola et al. "Esthelis, hyaluronic acid of Swiss design", *J. Med. Esth. Et Chir. Derm.* (2005)
- Extrait Brochure, Belotero
- Gold "Soft Tissue Augmentation in Dermatology", *Journal of Cutaneous and Aesthetic Surgery* (2010)

ANNUAL REPORT
1999

Q-MED

CONTENTS

THE YEAR 1999

Q-Med reports a net turnover of SEK 143.7 million (84.0) for 1999, an increase of 71%. Sales of aesthetic products increased by 84% to SEK 124.8 million (67.9).

Large investments were made in research and development. Due to the great sales expansion, operating income was 46% better than the previous year and amounted to SEK 18.2 million (12.5). Operating income before R&D expenses was SEK 41.4 million (19.8), an increase of 109%. Net income amounted to SEK 15.7 million (7.7), which means that earnings per share increased by 100% to SEK 0.86 (0.43).

On December 6 the Q-Med share was introduced on the O-list of the OM Stockholm Stock Exchange. In connection with the introduction a new share issue was carried out, which generated SEK 258 million net for Q-Med.

In September DEFLUX was approved (CE-marked) for the indication of stress urinary incontinence in women. In November CE-approval was obtained for PERLANE, Q-Med's product for facial contouring.

An agreement was reached with Ixion Biotechnology concerning cooperation on the transplantation of stem cells with the aim of curing insulin-demanding diabetes. Q-Med's NASHA gel will act as a protective barrier and encapsulating medium for the cells.

The cash flow from the current year's operations remained positive at SEK 14.1 million (14.1). SEK 28.1 million (38.6) was invested in new premises and production equipment. The new share issue at the end of the year meant that liquid funds amounted to SEK 250.6 million (2.8) at December 31, 1999. The equity/assets ratio amounted to 82.6% (44.9).

The number of employees increased from 77 to 110. In September a third personnel options programme was carried out. Per Olof Wallström took up the position of new President and Chief Executive Officer in April.

No dividend is proposed.

Background picture: NASHA gel

PRESIDENT'S STATEMENT

Per Olof Wallström
President and Chief
Executive Officer

Each year in Q-Med's short history has been marked by great changes, and never has this been more true than in 1999. December 6 was the company's first day of trading on the O-list of the Stockholm Stock Exchange. This milestone is of considerable significance for continued positive development. We now have the financial strength required to invest in new products and markets at the pace we desire. Furthermore, Q-Med's exposure supports the marketing of the company's products and facilitates the recruitment of new employees - this recruitment is a key factor for continued success.

Turnover increased by 71% in 1999 to SEK 144 million. The increase is primarily attributable to our aesthetics operations, which increased by 84% to SEK 125 million. This is due both to healthy growth in existing markets such as Brazil, Italy, Germany and France and to the establishment of new markets, where in particular sales of RESTYLANE in South Korea have developed positively.

In order to get our new products on to the market we are investing ambitiously, and this applies to research and development, clinical trials and documentation. These costs increased by 215%. Despite the strong expansion we can present an operating income which is 46% better than the previous year.

The process of taking Q-Med to the Stock Exchange provided us with experience that will be valuable for our future development. We were thoroughly analysed during the work on the introduction and our vision for Q-Med's future was chiselled out even more clearly. Strategies for the company's various business areas were set and the work of realizing our goals continued during the year in a more structured way than previously. All the business areas work with the NASHA (Non-Animal Stabilized Hyaluronic Acid) gels developed in-house for different clinical applications. Every new day confirms the strength of our technology and the goal to become a world-leader within injectable, degradable biomaterials feels very realistic. Seven success factors to reach this goal can be emphasized:

GLOBALIZATION OF THE AESTHETICS BUSINESS

The aesthetics business, where RESTYLANE is the main product, is today Q-Med's motor. During 1999 RESTYLANE was launched in Mexico, Argentina, South Korea and other countries. The product is now sold in more than 40 countries, with the emphasis on Europe, South America, Canada and Australia. We have our own sales companies in six major countries. The great challenge for 2000 will be the launch in Japan which is expected at the end of the year. The globalization will be complete with the planned introduction in USA during 2002.

At the beginning of 2000 two complementary products for facial aesthetics are to be launched, RESTYLANE FINE LINES for the filling out of finer lines and PERLANE for deeper facial folds as well as the contouring of the cheekbones and chin. Customers will thereby have access to a family of NASHA-based aesthetic products for different needs.

Within Aesthetics MACROLANE is also being developed, for minor breast augmentations. This involves a new treatment principle and in addition a new, complementary area to facial aesthetics for Q-Med. MACROLANE will undergo clinical trials during the year 2000 and it is expected that CE-marking, that is approval for sales in the EEA area, will be obtained in 2001.

EXTENSION INTO MEDICAL AREAS OF USE

Due to the successes within the aesthetics business Q-Med has been able to initialize activities in two complementary medical areas, orthopedics and urology. Documentation of DUROLANE is ongoing for use within above all arthritis in the knee. Because of the NASHA technology, DUROLANE is expected to be able to be given as a single dose and still have at least the equivalent clinical effect of the competing products with their 3 to 5 injections.

Within urology DEFLUX was CE-marked for stress urinary incontinence in women in September 1999. The substance has been approved for the treatment of vesicoureteral reflux in children since December 1998. DEFLUX will also undergo documentation studies for registration in USA. In order to be able to take the treatment of stress urinary incontinence from hospitals' specialist

departments to outpatient care, work has been begun on simplifying and documenting the technique which is used in connection with the implant.

OWN ORGANIZATION OR PARTNERSHIP

Within Aesthetics the main strategy is to set up our own subsidiaries in the major markets and to take full responsibility for sales and marketing vis-à-vis primarily dermatologists and plastic surgeons. Concerning the American market, evaluation of different alternatives for establishment there, including partnership, is being carried out. Within Orthopedics we have limited opportunities to reach outpatient care, where many arthritis patients are treated. Therefore the company will choose a partner for the commercialization of DUROLANE. Negotiations are expected to be begun in the middle of 2000 and the goal is to come to an agreement with a strategic partner before the end of the year.

Q-Med will also need a partner for DEFLUX within the field of stress urinary incontinence, above all when the new technique has been developed so that the product can be introduced into outpatient care. DEFLUX for VUR may also in the future be handled by a combination of our own subsidiaries and local distributors.

Our strategy is to finance all product development ourselves, including documentation and clinical trials, up to registration or CE-marking. Our future partners thus get a ready product to market. This means a greater capital investment for Q-Med initially, but should in return give us better contractual conditions.

TECHNICAL DEVELOPMENT - NEW PATENTS

The patent-protected NASHA process is the foundation of the company's technology base. We strive to continue to develop our processes and patents and thereby strengthen the intellectual property that Q-Med has through patents and knowledge capital. It is Q-Med's intention to produce for the world market from our hyper-modern facility in Uppsala.

A STRONG ORGANIZATION

During the year the company has been strengthened through the recruitment of more than 30 people, about 10 of them in senior positions. Competence has been broadened and deepened in all areas. During 2000 we will continue to expand within production, R&D, the business areas and the subsidiaries. We aim to further employ more than 40 people, which means that Q-Med should have approximately 150 employees at the end of the year.

STRONG CAPITAL BASE

Through the introduction on the OM Stockholm Stock Exchange SEK 258 million was generated for Q-Med. This capital makes it possible to proceed at the fast pace that we have set our minds on, both with clinical documentation and in the opening of new markets. The rapid growth is capital-demanding and furthermore we intend to make additional investments in our facilities in Uppsala in order to manage the expansion in volumes.

EXCITING AREAS OF RESEARCH

Over and above the projects which have already been described, Q-Med is cooperating with an American biotechnology company, Ixion Biotechnology, Inc. Ixion is a company which has specialized in finding and cultivating stem cells and letting them mature and form insulin-producing cells intended for transplantation. The cells are put into a NASHA gel and the hyaluronic acid gives the cells protection during the transplantation and the very early stages in the host organism. It has been successfully shown that the implanted cells take over the regulation of sugar in mice. The goal is to be able to offer a technology which allows insulin-demanding diabetes patients to function normally without daily doses of injected insulin. These initial trials have recently been published in Nature Medicine (March 2000, Volume 6, Number 3, pp 278-282).

Moreover, Q-Med has plans to make use of NASHA gels as carriers of pharmaceuticals or hormones and thereby attain a system for controlled release in the body. These trials are planned to be carried out together with one or more partners.

Our action plans within these seven areas constitute the base for Q-Med's continued strong development for many years to come. Our shareholders, who have grown to almost 9,000 through the introduction on the Stock Exchange and the spreading of ownership, can expect continued bold offensives. Q-Med's personnel and management will do their utmost to fulfil the vision of becoming world-leaders within degradable and injectable biomaterials.

Finally, I would like to thank everyone who has contributed to Q-Med's successes during the year. Without our devoted, loyal and extraordinarily competent personnel and a wise, challenging and supportive Board we would not have been able to carry out our plans with the precision and force that we have in fact achieved.

Per Olof Wallström
President and Chief Executive Officer

THIS IS Q-MED

Q-Med is a rapidly growing and profitable company which was started in 1987 with a view to commercializing the research that had been carried out by the founder, Bengt Ågerup. Since the end of 1995 the company has run its operations in their present structure, which is based on a new form of stabilized hyaluronic acid, developed and patented by Q-Med. Hyaluronic acid is a natural polysaccharide which is a part of the connective tissue that is to be found in all the organs in the body. Q-Med produces a non-animal and stabilized hyaluronic acid biosynthetically. This substance, which is the base of Q-Med's products, goes under the name of NASHA (Non-Animal Stabilized Hyaluronic Acid). Today the main part of Q-Med's sales are constituted by RESTYLANE, a product for the treatment and filling out of wrinkles and lips. Q-Med is ISO9001/EN46001-certified.

AIM

Q-Med develops, produces, markets and sells implants based on NASHA technology for aesthetic and medical use by doctors, clinics and institutions.

OBJECTIVES

Q-Med's long-term objective is to become the world-leader within the field of degradable and injectable biomaterials. The company will make use of its own NASHA technology to develop and commercialize NASHA-based products, in particular injectable implants within the areas of Aesthetics, Urology and Orthopedics.

Within the area of Aesthetics the objective is to by 2001 have submitted a file for the registration of RESTYLANE in the USA and to have obtained CE-marking for MACROLANE, a product for breast augmentation.

The objective for the area of Urology is to submit a file in USA and Japan for the registration of DEFLUX during 2000 for the indication of vesicoureteral reflux in children. In addition, the goal is that the file for the registration of DEFLUX for stress urinary incontinence in USA and Japan be submitted before the end of 2001.

With respect to Q-Med's third area, Orthopedics, the objective is to have DUROLANE, a new product for osteoarthritis, approved for marketing in Europe before the end of 2000. A registration file for the USA will be submitted during 2001.

During 2000 the company will meet the requirements that the American control authority, FDA, lay out in their GMP-QSR standard.

The Group's overall goal is that in the long term income before financial items will amount to at least 25% of the net turnover. The equity/assets ratio will not be less than 40%. For 2000 the turnover will be considerably greater than the turnover for 1999, while the strong focusing on new products and markets will mean that the operating margin will temporarily decrease. The gross margin will be improved through the strong increase in volumes and a more efficient production organization.

STRATEGY

Key factors in Q-Med being able to attain its objectives are that the company is successful in:

- **obtaining the necessary approvals from the authorities in order to introduce existing products in new geographical markets.**
  RESTYLANE, RESTYLANE FINE LINES, PERLANE and DEFLUX are CE-marked and are thus available for marketing in Europe. Q-Med intends to register these products for all important markets outside Europe.
- **identifying and developing further NASHA applications.**
  At present Q-Med is working with NASHA products for breast augmentation and osteoarthritis, for example. Furthermore, research is being carried out within explorative areas, above all cell therapy for the treatment of diabetes.
- **securing suitable channels for the marketing and distribution of various NASHA products and products under development.**
  Q-Med intends to use a combination of strategic alliances, direct sales and agents and distributors, depending on the conditions in each market. Within the aesthetics area the products will be distributed via subsidiaries or local distributors. With regard to DEFLUX for incontinence and DUROLANE, cooperation will be established with partners who already have marketing, distribution and sales channels within each product area targeting primary health care.
- **maintaining its technical competitive advantage.**
  Q-Med has patents in the USA which protect NASHA technology and has applied for patents in other important markets. Furthermore, highly detailed knowledge is required in order to recreate the manufacturing process for NASHA. Great emphasis

will be placed on defending existing patents, applying for new patents in other countries and securing other forms of protection. Furthermore, Q-Med will continue to refine its manufacturing processes and techniques for the stabilization of HA. As the product portfolio is expanded the intellectual property rights will be extended and more patents will be applied for when this is possible.

QUALITY POLICY AND QUALITY SYSTEM

Q-Med's quality policy is that the company will develop, document and manufacture products whose quality makes their intended use safe and effective. Delivery times and support will meet the customer's expectations.

The quality system that Q-Med has established is based on the following standards:

- SS-EN ISO 9001, Quality System - requirements for construction, development, production, installation and service,
- SS-EN 46001, Quality system - medical devices,
- cGMP (current Good Manufacturing Practices), GCP (Good Clinical Practices) and GLP (Good Laboratory Practices).

Furthermore, the new GMP-QSR (Good Manufacturing Practices - Quality System Regulations) standard which applies in the USA market is in the process of being implemented.

The company's notified body, in Q-Med's case the Swedish Medical Products Agency certification unit, carries out annual audits of the quality system.

The new production facility which was completed in Uppsala during 1999 involves greater automization of production, is equipped with the latest technology in the field and meets the appropriate quality requirements.

ORGANIZATION

Q-Med consists of the Parent Company Q-Med AB (publ) in Uppsala, Sweden, where the head office is situated and all production and product development take place. The wholly owned subsidiaries in France, Australia (with a branch office in New Zealand), United Kingdom, Germany, Canada and Italy (established 1999) act as sales companies. In the USA there is a dormant subsidiary. During 2000 a sales company will be started in Japan.

At the end of 1999 the organization consisted of 110 people, an increase of 33 people during the year. The foreign subsidiaries have also engaged a number of independent salesmen. For the most part personnel within research and development and administrative functions were employed. Today Q-Med has approximately 30 employees within research and development, about 20 employees within production and just as many in administration, as well as 40 people who work in the marketing and sales departments in Uppsala and in the subsidiaries. It is estimated that at the end of the year 2000 the number of employees will be approximately 150. Recruitment during the coming year will focus on development, production and marketing. Q-Med is organized in four major units:

- **Operations**, which includes the research and development departments, manufacturing and quality control. The products are then sold and marketed by one of the three following business units:
- **Aesthetics** with the products RESTYLANE, RESTYLANE FINE LINES and PERLANE for facial aesthetics. Development of MACROLANE for breast augmentation is ongoing.
- **Urology** with DEFLUX for vesicoureteral reflux (a malformation in the wall of the urinary bladder) in children and stress urinary incontinence in women.
- **Orthopedics** with DUROLANE, Q-Med's product for the treatment of joints which is under development.

During 1999 Q-Med's programme for competence and leadership development was intensified. It is intended that this will be both broadened and deepened during 2000.

THE Q-MED SHARE

LISTING AND NEW ISSUE

On December 6, 1999 the Q-Med share was listed on the O-list of the OM Stockholm Stock Exchange. In connection with this a spreading of ownership was carried out through a new issue of 3 million shares, corresponding to SEK 290 million. Furthermore an over-allotment option was exercised, which meant that the principal owners Agerup Holding and Health Cap KB sold 500,000 shares each. The new share issue was oversubscribed 5-fold. When issue expenses had been deducted the net funds for Q-Med amounted to SEK 258 million. The funds from the new share issue will be used to meet Q-Med's increased need for operating capital, which is governed by the company's continued growth, and to reduce the company's debts. Furthermore, the funds are intended to be used for investments to extend the company's manufacturing facilities for new products under development and for investments in and renovation of extended office premises. The company may also use some of the funds to exercise the option set out in the Ixion agreement (see page 20).

During the period from the listing until March 8, 2000 7.8 million Q-Med shares were traded to a value of SEK 598.9 million.

NUMBER OF SHARES AND SHARE CAPITAL

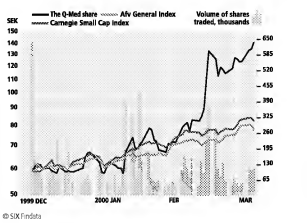
The number of shares in Q-Med AB (publ) amounted to 22,805,000 at December 31, 1999. All shares carry one vote and represent the same proportion of the company's assets and income. The par value is SEK 0.07 per share and the share capital amounts to SEK 1.6 million.

DIVIDEND POLICY AND DIVIDEND

Q-Med plans until further notice to keep the major part of future profits in order to finance its operations and future growth and does not expect to pay out any dividend in the foreseeable future. Before it makes its proposal concerning the appropriation of profits, the Board takes into consideration, amongst other things, the company's profits, financial position and liquidity needs.

For the financial year 1999 the Board proposes that no dividend be paid out.

DEVELOPMENT OF THE SHARE PRICE



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The issue price for the Q-Med share was SEK 58. From the day when it was first listed on December 6, 1999 up until December 31, 1999 the share had risen to SEK 67. The share price has risen further so far during 2000 and amounted to SEK 142.50 on March 8, 2000 corresponding to a market value of just over SEK 3.2 billion. The earnings per share amounted to SEK 0.86 (0.43) and the P/e ratio at year-end was 78. For definitions, see page 39.

OWNERSHIP STRUCTURE

Q-Med's major shareholders are presented in the table below. The percentage of institutional ownership of Q-Med amounts to approximately 13% of the share capital. The percentage of foreign ownership is just over 10%.

Shareholder	Number of shares	Shares and votes, %
Agerup Holding	13,900,000	61.0
HealthCap KB	775,000	3.4
Skandia	500,000	2.2
Banco Funds	294,900	1.3
Handelsbanken Funds	294,900	1.3
Investor	170,000	0.7
Anders Milton	157,500	0.7
Tomas Billing	154,500	0.7
Other shareholders	6,558,600	28.7
Total	**22,805,000**	**100.0**

Source: Securities Register Centre share register February 29, 2000.

Q-Med's shareholders' holdings on February 29, 2000 were distributed as follows:

Size	Number of shares, thousands	Number of owners	Shares and votes, %
1 - 500	1,246	7,369	5.4
501 - 1,000	745	841	3.3
1,001 - 5,000	1,145	478	5.0
5,001 - 20,000	793	70	3.5
20,001 - 50,000	939	29	4.1
50,001 - 100,000	767	10	3.4
100,001 -	17,170	15	75.3
Total	**22,805**	**8,812**	**100.0**

Source: Securities Register Centre share register February 29, 2000.

OPTIONS

At the beginning of 1997 call options were issued to the majority of the members of the Board. The call options were redeemed from Agerup Holding on February 18, 2000.

Options for subscription to 1,500,000 new shares were issued by Q-Med in 1997 for the benefit of HealthCap KB. The options were redeemed in March 2000 at an issue price of SEK 18.67 per share. Furthermore, HealthCap had 1,065,000 call options from Agerup Holding, and these were also redeemed in March 2000. After the utilization of its options HealthCap's holding in Q-Med amounts to 13.7% of the shares and votes.

A further 875,000 subscription options have been issued by Q-Med for the benefit of the company's personnel. 225,000 of the options were issued in 1997 and can be used to subscribe until October 31, 2000 at a price of SEK 16.67 per share plus an annual adjustment upwards of 4%. In a second options programme in 1998 300,000 options were issued. These can be redeemed up until December 31, 2001 at a price of SEK 28.00 per share plus an annual adjustment upwards of 4%. The remaining 350,000 options were issued in 1999 and can be used to subscribe from May 1, 2000 until September 30, 2002 at a price of SEK 168.00 per share plus an annual adjustment upwards of 4%.

In all, the subscription options can generate a maximum of just under SEK 108 million for Q-Med.

HYALURONIC ACID

GENERAL

Hyaluronic acid (HA) is a natural polysaccharide which was first isolated and defined in 1934, from the vitreous body of the eye. Two years later it was found that HA was an important component in man's joint fluid. Further research showed that HA is to be found in all tissue in vertebrates. It was also demonstrated that there was a connection between HA and a number of diseases, such as rheumatoid arthritis, cancer and a number of skin diseases.

The first product containing HA came in the 1960s and was used in eye operations. Since then a number of products have been launched and HA has proved its great medical value. Its consistency and tissue-friendliness allow HA to be used in many pharmaceutical products, for example skin-care products and products for eye surgery and osteoarthritis (damaged joints). As HA is destroyed by gastric enzymes when taken orally and is not absorbed through the skin, local injections in the skin, joints and eyes are the most efficient method of administration. To date more than 30 million patients have been treated with the substance in its different forms.

Hyaluronic acid's main function in the body is to bind water and to lubricate movable parts of the body like joints and muscles. It also has an important role in physiological functions such as transporting substances to and within cells. If non-stabilized HA is introduced as an implant in the body, it is broken down quickly and disappears within a couple of days.

HA raw material can be extracted either from tissue rich in hyaluronic acid, such as rooster combs, or biosynthetically through the fermentation of bacteria.

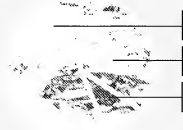
Q-MED'S HYALURONIC ACID - NASHA

Q-Med has chosen to use raw material produced biosynthetically in its products. The stabilized substance, which is the base of all of Q-Med's products, goes under the name of NASHA (Non-Animal Stabilized Hyaluronic Acid). The main advantages of NASHA are:

- its high level of purity, the absence of any virus of animal origin that might occur and the elimination of the allergic reactions which can arise from products of animal origin,
- stabilization, which prolongs the aesthetic or therapeutic effect of the products,
- its low manufacturing cost and
- the ability to create special properties in the various end products, which makes it possible to use the NASHA technology for many different areas of application.

This means that Q-Med's products do not require the patient to undergo a sensitivity test before the implant is introduced. Other advantages of the non-animal hyaluronic acid are that it can be produced in unlimited quantities and that it is easy to produce while still maintaining high quality. The raw material is supplied by external manufacturers and is modified so that it can be adapted for specific uses through Q-Med's purification and stabilization processes. The hyaluronic acid in the products is almost the same as that found in the body and is modified very little (0.5-1%). The NASHA gel is totally biologically degradable and is integrated naturally in the tissue so that important nutrients can pass freely through the implant.

Hyaluronic acid's distribution in the body



56%	in the skin
35%	in the muscles/skeleton
9%	elsewhere, for example synovial fluid, umbilical cord, blood, lymph

Patents and trademarks

Q-Med's technology is well protected through various patents. The most important patent, which protects the company's NASHA technology, is "Polysaccharide Gel Composition". This was applied for in the USA in 1995 and was granted there in 1998. The patent is also approved in Australia, New Zealand, Singapore and Hungary, and has been issued in Sudan. The patent application is at present being processed in Japan, Canada, Europe and other countries. No objections to the patent have been raised. In the USA the patent is valid until 2015.

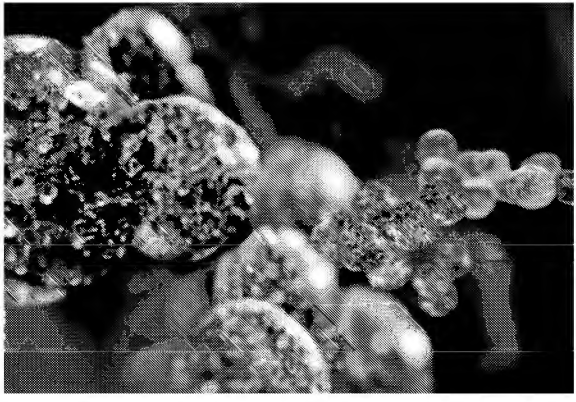
Q-Med's trademarks are RESTYLANE, RESTYLANE FINE LINES, PERLANE, MACROLANE, DEFLUX and DUROLANE.

Registration of products

Before Q-Med can start to market a product in the EU it must be approved and marked with the so-called Conformité Européenne Marque (CE-marked). The preconditions for having the product CE-marked are that the medical devices directive MDD 93/42 EEG is followed.

In the USA the approval of implantable medical devices is controlled by the regulations of the Food and Drug Administration (FDA). Implants are divided into three different classes, each with different requirements, depending on how high a risk the implant is considered to entail. The products may not be marketed or distributed before the investigatory phase has been completed, which comprises comprehensive clinical trials, and before the FDA has approved a so-called pre-market approval (PMA) application. How long the investigatory phase lasts is above all dependent on the scope of the clinical trials. The FDA's scrutinization process normally takes six to twelve months but can take longer and even be postponed indefinitely.

The Japanese regulations for implantable medical devices differ from those of the EU and the USA. In the rest of the world the authorities in most cases take very much into consideration whether the product has already been approved in one of the above countries.

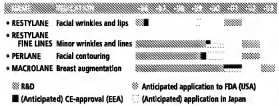


Concentrated hyaluronic acid.

AESTHETICS

PRODUCTS

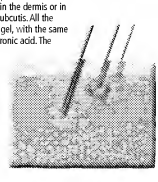
The HA products which are on the market today within the aesthetic area focus on facial aesthetics. At present Q-Med has three approved products for facial aesthetics, and these constitute a family of products to meet different correction needs.



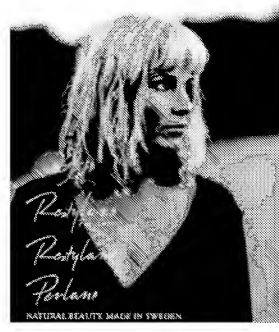
Product portfolio and products under development.

The dermis is the middle layer of the skin and contains the body's natural HA. It is strong tissue, and contains the many structures which are embedded in the skin, for example blood vessels, nerves and hair roots. HA in the dermis together with water constitute the skin's volume. An obvious effect of ageing on the skin is that the body's natural HA decreases. Q-Med's facial aesthetic products are injected into the dermis and give volume where the concentration of the body's own hyaluronic acid has decreased. One treatment session takes a maximum of 30 minutes. The results are immediately noticeable and leave no scars or other traces on the face. One to two days after the treatment redness and swelling in the treated area can, however, possibly occur. Other types of reaction are very unusual.

The products are, like all of Q-Med's products, degradable. Due to the very effective stabilization method, however, the volume is kept intact even if the hyaluronic acid slowly disappears, since water takes it place. The less concentrated the gel is, the more water each molecule can bind, so-called isovolemic degradation.

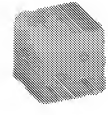


Q-Med's three different products for facial aesthetics. For thin, superficial lines in the upper part of the dermis RESTYLANE FINE LINES is used. For somewhat deeper wrinkles in the middle layer of the dermis RESTYLANE is used. PERLANE is used for more pronounced facial folds and is injected deep down in the dermis or in the most superficial part of the subcutis. All the products are based on the same gel, with the same concentration of stabilized hyaluronic acid. The difference between the products is the size of the gel particles. Each product should be injected at different levels in the skin in order to obtain the right effect. The different layers of skin have a different tissue structure and the different gels are designed to match these different structures.



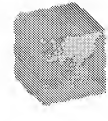
RESTYLANE

RESTYLANE, which is Q-Med's first and longest-used product, is intended for the filling out of lips and for the treatment of facial wrinkles. So far over 200,000 patients have been treated. The patented stabilization method means that the product has a longer-lasting effect than competing products. Clinical studies show that RESTYLANE is effective up to one year after the treatment of wrinkles and half a year after the filling out of lips.



RESTYLANE FINE LINES

Q-Med has also developed RESTYLANE for further areas of use. RESTYLANE FINE LINES has a more even consistency which can be injected with the aid of a thinner needle and is intended for the treatment of finer wrinkles in the face.



Q-Med's facial aesthetic products maintain their volume for a long time as the gel can bind more water the less concentrated it is.

In order to ensure that Q-Med's facial aesthetic products give optimal clinical results, courses are arranged regularly. Here a course in injection techniques is being run with the Norwegian doctor Stein Tveten as course leader.

PERLANE

PERLANE is yet another modification of RESTYLANE, and is intended for somewhat deeper injections in order to allow correction of the shape of the face and of more noticeable facial folds and scarring.

MARKET

The world market for injectable products for facial aesthetics is today estimated to amount to between SEK 1.5 and 2 billion per year. New, improved and more varied products mean that there is considerable growth in this market. The USA is the largest market and increased according to research by 27% from 1997 to 1998.

Today RESTYLANE has been launched in a great many countries. During 1999 the product was approved in Argentina, Australia, Peru, Poland and South Korea. The next objective is to have the product approved so that it can be also launched in Japan and the USA. RESTYLANE FINE LINES and PERLANE will be launched at the end of the first quarter in 2000.

Q-Med's marketing strategy is to create a high level of consciousness regarding the products among customers so that they will have the opportunity and the knowledge to influence the choice of treatment method themselves. In Australia (covers New Zealand as well), France, Italy,

Q-Med's facial aesthetic products are today sold in more than 40 countries.

Canada, Great Britain and Germany Q-Med has wholly owned sales companies. In addition there are 24 distributors who have exclusive rights for 31 countries in all. Q-Med will continue to market its facial aesthetic products both through its own subsidiaries and through external distributors. The company's own subsidiaries will be used in the highest priority markets.

Direct competitors to Q-Med's products within facial aesthetics are products which are sold primarily by the American company Collagen Aesthetics, Inc., which was recently acquired by Inamed Corp. Other forms of treatment such as laser treatment, chemical peeling, fat injections, derm abrasions and injections of botulinum toxin compete to a certain extent.

RESEARCH AND DEVELOPMENT
MACROLANE

Q-Med is working on developing a new product for breast augmentation, MACROLANE. This is manufactured using NASHA with large, compact gel particles. Unlike existing products, which consist of implantable bags, MACROLANE is intended to be injected direct into the breast tissue for minor augmentations (up to approximately 100 ml). The implant is expected to have a residence time of up to two years.

Market

The market for breast operations is growing very rapidly. In the USA aesthetic breast augmentation treatment was carried out on more than 130,000 people during 1998. 70,000 patients underwent breast reconstruction. The USA market for the implants themselves is estimated to be SEK 1-2 billion. The American companies McGhan Medical, Inc. (subsidiary of Inamed Corp.) and Mentor, Inc., which both primarily market breast implants filled with sodium chloride solution, together account for most of the market.

MACROLANE will not directly compete with existing products, but addresses a new market. The technology involving MACROLANE addresses the growing trend within the cosmetic area of carrying out treatment in outpatient care under local anesthetic. The development of new techniques and simpler forms of treatment will probably increase the demand for cosmetic implants from patients who value the convenience of quick treatment and a short period of convalescence.

MACROLANE will, like the facial aesthetic products, be sold both through the company's own subsidiaries and external distributors.

UROLOGY

PRODUCTS

At present Q-Med has two approved products within the area of Urology. The NASHA gel DEFLUX is a urological application of Q-Med's hyaluronic acid technology which is used in the treatment of vesicoureteral reflux (VUR) in children and stress urinary incontinence in women. The gel is a copolymer between NASHA and dextranomer, which is a crosslinked polysaccharide that promotes the natural formation of connective tissue. This is necessary to prolong the volume-creating effect of DEFLUX, which has a long degradation period, 3 - 5 years.

Product portfolio.

DEFLUX - VUR

Vesicoureteral reflux, VUR, is a condition primarily in small children which leads to urine leaking from the urinary bladder back into the kidneys via the ureter, which in the long term can lead to irreversible kidney damage. DEFLUX is injected using the keyhole technique into the wall of the urinary bladder in order to improve the valve mechanism at the opening of the ureter. This method can spare many children a major operation or the cost and trouble of years of treatment with antibiotics. In clinical trials which have comprised around 500 patients this new implant has proved to be highly competitive when compared with existing injectable materials which are used for endoscopic treatment of VUR. Long-term follow-up suggests that over 80% of the children manage to develop their own valve mechanism during the time the implant remains in the body, so that further treatment is not necessary.

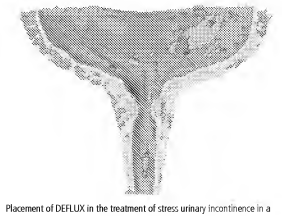
Placement of DEFLUX in the bladder wall.

Dr. Göran Läckgren and Dr. Arne Stenberg, child urologists at Uppsala's University Hospital, have treated approximately 500 children with DEFLUX for VUR. "Treatment with DEFLUX is an easy and safe method for the patient".

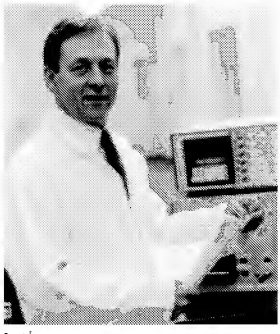
DEFLUX - Stress urinary incontinence

Urinary incontinence is a big health problem both because of its common occurrence and the great inconvenience that it entails, both physically and mentally. Stress urinary incontinence (SUI) means that urine involuntarily leaks out during physical exercise or upon coughing, sneezing or laughing. A common cause of stress urinary incontinence is that the muscle power around the upper part of the urethra has been weakened. DEFLUX is injected under the mucous membrane of the urethra, which creates increased tissue mass and thus improves the resistance mechanism. The results from initial clinical trials are positive.

In order to be able to take the treatment from hospitals' specialist departments to outpatient care, work has been begun on simplifying and documenting the technique which is used in connection with the implant.



Placement of DEFLUX in the treatment of stress urinary incontinence in a woman.



Bengt Ågerup

Bengt Ågerup develops a device for a new injection technique

Bengt Ågerup is Q-Med's founder. Up until April 1999 he was also the company's Managing Director, but he has now gone over to working full time on his passion, research and development within the area of hyaluronic acid. One of his exciting projects is the development of a completely new device for the injection of DEFLUX in the treatment of stress urinary incontinence in women. Bengt explains the background:

"Stress urinary incontinence in women is a very common complaint. Incontinence troubles up to 30% of all women after menopause. Today stress urinary incontinence in women is treated with implants such as DEFLUX only in specialist departments in hospitals. The health service would become seriously strained if everyone suffering from incontinence were to demand that they be actively treated. We are therefore developing an injection device which aims to enable quick, simple treatment by the woman's own gynecologist or a specialized general practitioner. This would make the treatment generally available in a way that is certainly not the case today. We have developed a prototype which will be tested during the year. If this is successful we will be able to offer both DEFLUX and the injection device in a kit. Once this is ready help for stress urinary incontinence can be taken to outpatient care, which can then treat the majority of the patients."

MARKET

VUR occurs in approximately 1% of all children and about half of these need some form of treatment. An estimate of the present world market for endoscopic treatment of VUR is more than SEK 100 million per year. Q-Med's product for VUR is today sold in more than 10 markets, mainly in Europe.

Stress urinary incontinence, which is the most common type of incontinence, affects almost exclusively women. It is estimated that approximately 30% of all women over the age of 50 have an incontinence problem. More than 5% of the population over 60 has more severe problems and need some form of treatment. Today the commonest methods of treatment for stress urinary incontinence are pelvic muscle training and bladder training. Other methods include different injectable volume-increasing materials such as teflon, silicone paste, microballoons and collagen from cow's hide. When this does not have sufficient effect or gives unacceptable side-effects, more complicated methods of treatment are used, such as surgery. DEFLUX has the potential to become a significant product in the treatment of stress urinary incontinence, especially if Q-Med is successful in simplifying the injection technique. Pelvic muscle training and bladder training often give insufficient results and other injectable products have proved to have considerable disadvantages. Teflon, silicone paste and microballoons contain non-degradable particles. The use of collagen in stress urinary incontinence is decreasing, as the product cannot meet existing demands for a safe and long-acting implant.

As the incidence of incontinence increases with age and the percentage of old people is increasing, the market for incontinence treatment will also further increase. If Q-Med is successful in simplifying the method of treatment, the market potential is judged to be very great. Today the market for the treatment of incontinence through an implant is largely in the USA. According to research, 13 million Americans, and 85% of these are women, suffer from incontinence. Collagen to a value of SEK 250 million was used in the treatment of stress urinary incontinence in the USA during 1998. The American company Bard, Inc. has the greatest share of the market.

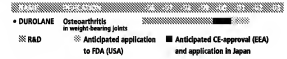
DEFLUX for VUR is sold through the company's own subsidiaries and local distributors. Regarding the distribution of DEFLUX for stress urinary incontinence, Q-Med intends to look for a corporate partner.

ORTHOPEDICS

RESEARCH AND DEVELOPMENT

Osteoarthritis (OA) is a very painful and disabling disease which is characterized by gradual degradation of the articular cartilage. The disease generally affects older people, but sports injuries, for instance, can also lead to OA. The knee and hip joints, which bear the body's weight, are the ones most often affected. In the joints HA helps the cartilage to take the strain brought about by the carried weight and the joint's movements. The body's HA also constitutes a natural part of the joint fluid, which lubricates cartilage and ligaments and affords a protective environment which promotes optimal cell function in the mucous membrane.

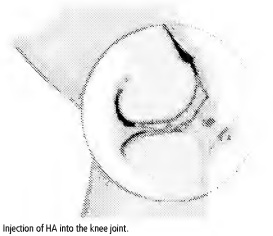
A great deal of the research around OA has focused on cartilage and bones. However, it has been known for some time that the joint fluid in joints affected by OA has a much lower viscosity and elasticity than in healthy joints. Therefore OA is now also treated by injecting HA into the joints in order to restore the joint fluid's elasticity and viscosity. These injections can reduce the pain and improve the mobility of the joint without the side-effects associated with existing alternative methods of treatment. The products which are on the market today, however, use primarily HA of animal origin as the raw material and all of them require repeated injections (3-5) in each round of treatment.



Products under development.

DUROLANE

Durolane is Q-Med's NASHA product which is under development for the treatment of osteoarthritis, and it is intended for just one injection per treatment. The product will be injected into the joint, where it can remain for up to one month, which corresponds to the longest treatment cycle with treatments involving several injections. During this time NASHA is released slowly in the affected joint. Q-Med intends to document that DUROLANE eases pain and increases mobility in the affected joint for at least six months. Preliminary trials indicate that DUROLANE has a long-lasting favourable effect.



Injection of HA into the knee joint.

Market

Osteoarthritis is considered to be one of the world's most common joint diseases. Investigations show that approximately 33 million people in the seven large pharmaceutical markets France, Italy, Japan, Spain, Great Britain, Germany and USA suffer from OA. An estimated 8 million people in the USA were affected by OA in the knee joint in 1998. The world market for injectable HA products for treatment of OA is today estimated at approximately SEK 5 billion and is to be found mainly in the USA and Japan. The market is judged to have very great growth potential, not least because of demographic factors.

Which form of treatment is used in cases of OA depends on how badly affected the patient is. The first step can be to lose weight and strengthen the muscles through physical training. The next step is some form of medical treatment, where doctors can prescribe non-steroid anti-inflammatory drugs or analgesics (Cox-2-inhibitors). In more severe cases of OA, when the mobility of the joint decreases, doctors may inject steroids into the joint in order to reduce the inflammation and ease the pain. This is effective but in general has an effect only for a short period. Furthermore, repeated use can be associated with degradation of the cartilage in the joint and can give negative metabolic effects in the body. When OA progresses to a stage where the cartilage layer has been considerably reduced the consequence is often appreciably reduced mobility and great pain in the joint. At this stage an orthopedic surgeon can carry out arthroscopy (keyhole surgery) in order to reduce an inflamed mucous membrane or to otherwise remove degraded cartilage and waste products from the knee joint

and perhaps finally replace the OA-affected joint with an artificial joint.

HA injections can be used as an alternative form of treatment both early or later in the course of the disease, often in combination with other pain-relieving drugs. The mechanism of action for HA has not been investigated in detail but the injected HA is presumed to replace the body's own HA as a lubricant and shock absorber and to be incorporated in cartilage surfaces.

Direct competitors of Q-Med in this area are, for example, Japan's Seikagaku, USA's Biomatrix, Scotland's Fermentech and Italy's Fidia. DUROLANE could also compete with, or alternatively be used together with, Cox-2-inhibitors. Major players in this area are, for example, the American companies Monsanto (in the process of merging with Pharmacia & Upjohn), Pfizer and Merck.

Regarding the distribution of DUROLANE, Q-Med intends to look for a strategic partner. Negotiations are expected to be begun in the middle of 2000 and the goal is to come to an agreement with a partner before the end of the year.

FUTURE INDICATIONS

Q-Med's NASHA technology makes it possible for cells and other substances to be encapsulated in NASHA gel and thereby be protected from attack by the patient's immune system. This encapsulating technique can enable the creation of new products within both cell therapy and drug delivery vehicles.

CELL THERAPY

At present Q-Med is evaluating, in cooperation with an American biotechnology company, Ixion Biotechnology, Inc., the use of NASHA in order to give protection and a developmental environment for progenitor stem cells in connection with the implantation of these cells in host organisms. These stem cells are differentiated into cell islets which have the ability to produce insulin after implantation. The enveloping in NASHA is considered to foster the cells' growth so that these cells can begin to control the uptake of glucose in insulin-dependent diabetics. Trials have been carried out in mice with positive results and have been recently published in the journal Nature Medicine (March 2000, Volume 6, Number 3, pp 278-282).

DRUG DELIVERY VEHICLES

Q-Med has plans to make use of NASHA gels as carriers of drugs or hormones and thereby achieve a system for controlled release in the body. These trials are planned to be carried out together with one or more partners.

REPORT OF THE BOARD OF DIRECTORS

Business

Q-Med develops, manufactures and sells medical implants based on NASHA (Non-Animal Stabilized Hyaluronic Acid). The company's customers are mainly doctors or other authorized users or institutions. At present there is marketing of RESTYLANE, which is used for the treatment of wrinkles and folds in the face and to increase the volume of the lips, RESTYLANE FINE LINES for the filling out of finer lines and PERLANE for deeper facial folds and for contouring of the cheekbones and chin. DEFLUX is also marketed, a product which is used for the treatment of vesicoureteral reflux (VUR) in children and stress urinary incontinence in women. All products are CE-marked, that is approved for sales within the EEA area. The majority of sales are constituted by RESTYLANE. The Group consists of the Parent Company Q-Med AB (publ) and a number of subsidiaries which sell the company's products in their respective markets.

New share issue and listing on the O-list of the OM Stockholm Stock Exchange

The Q-Med share was listed on the O-list of the OM Stockholm Stock Exchange on December 6, 1999. In connection with this a new share issue of 5 million shares, corresponding to SEK 290 million, was carried out. In order to obtain a good distribution of the shares the old shareholders' preferential rights were deviated from. The new share issue was oversubscribed 5-fold. The number of shareholders amounted to just below 9,000 at February 29, 2000, consisting of a large number of private persons and institutional investors. After the deduction of issue expenses the net liquid funds for Q-Med amounted to SEK 258 million. The funds shall secure continued strong growth and will, amongst other things, be used both to meet the increased need for operating capital, product launches and the building up of distribution companies in the USA and Japan, and for research and development.

New President and Chief Executive Officer

On April 1, 1999 Per Olof Wallström took up the position of President and Chief Executive Officer of Q-Med. He succeeded Bengt Ågerup, Q-Med's founder and principal owner, who is now the head of research and development. Per Olof Wallström has worked within the pharmaceutical industry for more than 27 years and he came to Q-Med from Bristol-Myers Squibb, where his position was President Northern, Central and Eastern Europe.

Research and development

Q-Med focuses its research and development on a range of NASHA-based applications, including products for breast augmentation and osteoarthritis and other areas of use such as cell therapy and drug delivery vehicles.

Cooperation agreement with Ixion Biotechnology

In accordance with an agreement between Q-Med and the American research and development company Ixion Biotechnology, Inc., Q-Med has undertaken to supply its NASHA gel to Ixion as an encapsulating material for Ixion's progenitor stem cells and to finance Ixion's research in exchange for a participating interest. Q-Med has pledged to acquire shares for USD 75,000 per month until the agreement is terminated or until Q-Med exercises the option as described below. At December 31, 1999 Q-Med had acquired shares for USD 675,000, corresponding to approximately 11.5% of the outstanding shares in Ixion. The option, which falls due on July 1, 2000, gives Q-Med the right to acquire either 2,700,000 shares in Ixion or a total of 50% of Ixion's share capital at the point in time for the exercising of the option for a price of USD 2 per share. Q-Med can at any time terminate the agreement by giving 90 days' notice. Both parties have the right to terminate the agreement on July 1, 2000 if the option is not exercised. Ixion had a booked negative shareholders' equity of USD 1.8 million and assets of USD 0.6 million at December 31, 1999. For 1999 Ixion reports a loss of USD 1.1 million.

Legal dispute with Biomatrix

On September 28, 1999, Biomatrix, Inc. and certain of its affiliates, and Bengt Ågerup, Q-Med AB, and certain affiliates of Q-Med reached a settlement (the "Settlement") of a lawsuit (the "Lawsuit") that was commenced by Biomatrix in the United States District Court for the District of New Jersey on May 3, 1999. The Settlement, in which none of the parties to the Lawsuit admitted any liability, included the grant of an exclusive, world-wide, fully paid-up and royalty-free license for certain technology

from Q-Med to Biomatrix. The technology subject to the License Agreement is unrelated to the technology underlying Q-Med's RESTYLANE product (U.S. Patent No. 5,827,937 and its foreign counterparts). Q-Med also agreed to pay Biomatrix a one-time payment of USD 100,000 and a 6% royalty on Q-Med's sales of certain products in the United States up to a maximum of USD 5.0 million. As part of the Settlement, the Lawsuit was dismissed, subject to being recommenced only in the event of a material breach by Q-Med of the agreements relating to the Settlement.

Distribution agreement concerning Venofer discontinued

Venofer is an intravenous iron preparation that, amongst other things, is given to dialysis patients in combination with a hormone. In accordance with a five-year exclusive licensing agreement with the Swiss manufacturer Vifor International, Inc., Q-Med had the right to sell Venofer in Sweden. For other Nordic countries there were semi-exclusive sales rights. The agreement expired on December 31, 1999. Q-Med therefore does not distribute Venofer as from January 1, 2000.

Future development

Q-Med strives to become a global company within several priority product areas, all based on NASHA. Q-Med's long-term objective is to be the world-leader within injectable, degradable biomaterials. This will be achieved through globalization of the aesthetics business and development and commercialization of competitive products within osteoarthritis and incontinence.

For the year 2000 the gross margin will be improved and sales will considerably exceed the figures for 1999, while the strong focusing on new products and markets will mean that the operating margin will temporarily decrease. Q-Med's product for the treatment of osteoarthritis is expected to be CE-marked in the fourth quarter of 2000. Two complementary products within facial aesthetics, RESTYLANE FINE LINES and PERLANE, are to be launched in a large number of markets during March 2000.

The work of the Board

The Board has met on twelve occasions during 1999. In addition, parts of the Board have met on a number of occasions to discuss questions that they have been requested to investigate further. Questions that the Board has dealt with during the year include major investments, financing needs and financing methods, the appointment of a new President and Chief Executive Officer, the new share issue, the listing on the Stock Exchange, and external information. For information on the people who are members of the Board, see page 41.

Proposed disposition of earnings

The Group's non-restricted equity amounted to SEK 18.2 million on December 31, 1999. No allocation to restricted equity is proposed. The Board and the Managing Director propose that the earnings at the disposal of the Annual General Meeting, consisting of retained earnings of SEK 11.5 million and a net profit of SEK 16.8 million, in total SEK 28.3 million, be carried forward.

CONSOLIDATED INCOME STATEMENT AND COMMENTS

SEK thousands	Note	1999	1998
Net turnover	1	143,658	84,042
Cost of goods sold	2, 14	-22,512	-18,196
Gross income		**121,146**	**65,846**
Selling expenses	2, 14	-65,086	-36,216
Administrative expenses	2, 14	-16,872	-8,985
Research and development costs	2, 14	-23,130	-7,347
Other operating revenues	3	2,941	2,124
Other operating expenses	4	-759	-2,970
Operating income		**18,240**	**12,452**
Result from financial items	5	-1,106	-572
Income after financial items		**17,134**	**11,880**
Taxes	6	-1,436	-4,184
Net income for the year		**15,698**	**7,696**

Revenues

Q-Med reports a net turnover of SEK 143.7 million (84.0) for 1999, an increase of 71% over the previous year.

Within Aesthetics sales are dominated by RESTYLANE, Q-Med's first approved product. Sales of RESTYLANE increased to SEK 122.3 million (67.9), an increase of 80% and corresponding to 85% (81) of the total net turnover. The increase in sales is due both to healthy growth in existing markets and to the establishment of operations in new markets. RESTYLANE is today marketed in more than 40 markets, where Brazil, Italy, Germany and France are the dominant countries. Amongst the new markets, growth was greatest during 1999 in South Korea and the Latin American countries.

In the late autumn of 1999 there were some initial sales of PERLANE, Q-Med's new product within facial aesthetics. The international launch will be in March 2000.

Turnover within Urology decreased from SEK 3.7 million to SEK 2.1 million, due to a loss of financing within research and development when a licensing agreement concerning potential urology products was discontinued in May 1998. Sales of the product DEFLUX increased from SEK 1.4 million to SEK 2.1 million. During the year DEFLUX has been sold in more than ten countries, primarily Sweden, Finland and Turkey. It is above all DEFLUX for the indication VUR that has generated sales. The use of DEFLUX in stress urinary incontinence was only CE-marked during the autumn of 1999 and contributed only marginally to sales.

Sales by the subsidiaries are dominated by RESTYLANE purchased from the Parent Company. England and Germany have had sales of DEFLUX during the year, but still on a small scale. Sales to the subsidiaries comprised SEK 34.8 million (18.5) of the Parent Company's total sales.

In addition to sales of NASHA-based products, the net turnover includes sales of Venofer, the iron preparation which Q-Med has sold under licence. During 1999 Venofer constituted SEK 16.9 million (12.4) of the Group's turnover. Q-Med does not distribute Venofer as from January 1, 2000, as the distribution agreement with Vifor has ceased to be valid.

Other revenues are comprised primarily by the writing off of a loan of SEK 2.2 million from the Swedish National Board for Industrial and Technical Development, NUTEK. Instead a royalty agreement has been signed concerning certain technology which is not related to the NASHA technology. The write-down is in the form of a lump sum.

The table below shows the net turnover for 1999 (1998) divided up per business area.

(SEK millions)	Aesthetics	Urology	Venofer	Total
Net turnover	124.8 (67.9)	2.1 (3.7)	16.8 (12.4)	143.7 (84.0)

Expenses and income

The cost of goods sold amounted to SEK 22.5 million (18.2). In addition to direct and indirect production costs for the NASHA-based products and purchasing costs for Venofer, this item also includes costs for quality control and documentation. The gross margin improved from 78.3% to 84.3%, above all as a consequence of the increased volumes of RESTYLANE and the reduced proportion of Venofer, which has a higher materials cost. The new production facilities which were started up in 1999 and ongoing process development projects are expected to further lower production costs during the coming years.

In addition to costs for the Parent Company's marketing function, the Group's selling expenses include all of the subsidiaries' indirect costs. Costs increased by 80% during 1999 due to the focus on continued sales expansion. Administration expenses consist of costs for the Parent Company's management as well as for the financial and administrative functions. Lawyers' costs of SEK 1.3 million resulting from a legal dispute that was settled in the USA are included in the year's figures. Research and development costs consist of costs both for work on the new products and for documentation and clinical trials for existing products to be sold in USA and Japan. The great focus on expansion meant that costs for research and development increased to 16% (9) of the net turnover.

Depreciation and amortization to the tune of SEK 6.7 million (2.9) have been divided among the various functions. The operating margin amounted to 12.7% (14.8).

The table below shows a summarized income statement for 1999 (1998) divided up per quarter.

	Jan - Mar		Apr - June		July - Sept		Oct - Dec		Total	
SEK millions	1999	1998	1999	1998	1999	1998	1999	1998	1999	1998
Net turnover	29.8	13.4	36.2	22.7	32.8	21.6	44.9	26.3	143.7	84.0
Gross income	25.4	10.4	30.7	17.6	27.1	18.4	37.9	19.4	121.1	65.8
Selling expenses	-12.3	-5.7	-15.9	-6.1	-14.6	-9.9	-22.3	-14.5	-65.1	-36.2
Adm. expenses	-4.2	-2.7	-3.4	-3.1	-4.5	-1.8	-4.8	-1.4	-16.9	-9.0
R&D costs	-4.1	-1.2	-5.0	-1.7	-6.2	-1.6	-7.8	-2.8	-23.1	-7.3
Other operating revenues/expenses	1.9	0.7	0.3	0.0	-0.5	0.9	0.5	-2.4	2.2	-0.8
Operating income	6.7	1.5	6.7	6.7	1.3	6.0	3.5	-1.7	18.2	12.5

Continued investments have been partly financed through increased bank credit. Net financial income thereby deteriorated, from SEK -0.6 million to SEK -1.1 million. Income after financial items amounted to SEK 17.1 million (11.9), an increase corresponding to 44%. Tax costs for the year amounted to SEK 1.4 million (4.2), of which current tax was SEK 0.3 million (2.6). The Parent Company's costs for the new share issue which was carried out in December (SEK 32.1 million) have not been charged against income for the year, but have been offset by an issue premium before being transferred to restricted reserves. However, tax relief will be claimed for these costs, and consequently the Parent Company is not liable to pay any tax for the financial year 1999.

The profit margin amounted to 10.9% (9.2). For more key ratios and definitions, see page 39.

CONSOLIDATED BALANCE SHEET AND COMMENTS

SEK thousands	Note	Dec 31, 1999	Dec 31, 1998
ASSETS			
Fixed assets			
Intangible assets			
Capitalized R&D expenses	2	-	53
Patents and other intellectual property	2	987	233
Goodwill	2	5,326	6,174
Tangible assets			
Buildings and land	2	41,892	33,121
Plant and machinery	2	22,970	12,485
Equipment, fixtures and fittings	2	6,218	4,645
Ongoing new facility and advance payment to suppliers		4,879	3,016
Financial assets			
Other financial assets		5,758	-
Other long-term receivables		608	643
Total fixed assets		**88,638**	**60,370**
Current assets			
Inventories			
Raw materials and consumables		6,926	3,093
Finished products and goods for resale		2,792	2,262
Current receivables			
Accounts receivable		26,026	13,938
Other current receivables		4,728	3,992
Prepaid expenses and accrued revenues		1,312	531
Cash and bank deposits		250,571	2,778
Total current assets		**292,355**	**26,594**
TOTAL ASSETS		**380,993**	**86,964**

Assets

Assets increased during the period from SEK 87.0 million to SEK 381.0 million, including fixed assets which increased from SEK 60.4 million to SEK 88.6 million.

Gross investments in building and land amounted to SEK 10.1 million (24.1), comprising the purchase of a neighbouring property in Uppsala. Refurbishment of the property was begun during 1999. SEK 4.1 million of the balance sheet item Ongoing new facility and advance payment to suppliers comprises this refurbishment. The premises will be used for further offices and for a smallish printing facility, so that existing premises can be better used within research and production. In December 1999 building work was also commenced on a high store next to the production facilities.

New production equipment was purchased for SEK 13.1 million (11.5), primarily comprising an automated filling and packaging line. Investments in other equipment amounted to SEK 3.4 million (2.7), largely comprising computers and office equipment. The cooperation agreement with Ixion Biotechnology, Inc. (see page 20) involves a continuous financial investment which at the end of the year amounted to SEK 5.6 million (-).

The cash flow from the current year's operations amounted to SEK 14.1 million (14.1) and the cash flow from investment activities amounted to SEK -35.0 million (-48.1). As a consequence of the new share issue in December the total cash flow for the year was positive, SEK 247.8 million (-16.1).

Current assets increased from SEK 26.6 million to SEK 292.4 million, due above all to the funds generated by the new share issue, but also because of increased accounts receivable. The average stock was 6% (5) of the year's net turnover, while the corresponding figure for accounts receivable was 15% (16).

SEK thousands	Note	Dec 31, 1999	Dec 31, 1998
LIABILITIES AND SHAREHOLDERS' EQUITY			
Shareholders' equity	8		
Restricted shareholders' equity			
Share capital		1,596	1,187
Restricted reserves		295,086	32,330
Unrestricted shareholders' equity			
Unrestricted reserves		2,479	-2,135
Net income for the year		15,698	7,696
Total shareholders' equity		**314,859**	**39,078**
Provisions		**5,232**	**4,314**
Long-term liabilities	10, 12		
Overdraft facility utilized		-	17,951
Loans from STU* & NUTEK**		-	1,601
Liabilities to credit institutions		26,922	-
Total long-term liabilities		**26,922**	**19,552**
Current liabilities			
Liabilities to credit institutions	11, 12	6,023	4,500
Accounts payable		12,255	9,818
Tax liabilities		202	2,607
Other current liabilities		3,829	1,703
Accrued expenses and prepaid revenues		11,671	5,392
Total current liabilities		**33,980**	**24,020**
TOTAL LIABILITIES AND SHAREHOLDERS' EQUITY		**380,993**	**86,964**
Collateral to secure own liabilities	12	55,100	25,100
Contingent liabilities		-	-

* National Swedish Board for Technical Development
** Swedish National Board for Industrial and Technical Development

Liabilities and shareholders' equity

Interest-bearing liabilities increased by SEK 9.0 million due to the year's comprehensive investments. A loan from STU & NUTEK (National Swedish Board for Technical Development and Swedish National Board for Industrial and Technical Development) was written off during the year, which generated a one-off revenue. The debt/equity ratio decreased from 0.6 times to 0.1 times. For more key ratios and definitions, see page 39.

Average accounts payable were 5% (9) of the year's net turnover. The item Provisions consists partly of deferred tax of SEK 3.4 million (2.3) and partly of provision for a VAT dispute in France from 1998 to the tune of SEK 1.8 million (2.0).

Shareholders' equity increased due to the new share issue (SEK 257.9 million), an options programme for the employees (SEK 2.1 million) and the net income for the period (SEK 15.7 million).

CONSOLIDATED CASH FLOW ANALYSIS

SEK thousands	Note	1999	1998
Operating activities			
Income after financial items		17,134	11,880
Adjustments for items not included in the cash flow, etc.	13	6,506	4,967
Tax paid		-3,703	-5,241
Cash flow from operating activities before changes in working capital		**19,937**	**11,606**
Increase(-)/Decrease(+) in inventories		-4,365	-3,380
Increase(-)/Decrease(+) in trade receivables		-12,192	-2,342
Increase(+)/Decrease(-) in trade payables		10,754	8,198
Cash flow from operating activities		**14,134**	**14,082**
Investing activities			
Acquisition of intangible fixed assets		-853	-6,848
Acquisition of tangible fixed assets		-28,422	-41,252
Acquisition of financial assets		-5,695	-
Cash flow from investing activities		**-34,970**	**-48,100**
Financing activities			
Proceeds from issuance of share capital		259,648	-
Proceeds from borrowings		26,932	17,951
Repayment of borrowings		-17,951	-
Cash flow from financing activities		**268,629**	**17,951**
Cash flow for the year		**247,793**	**-16,067**
Cash and bank deposits at beginning of year		2,778	18,845
Cash and bank deposits at end of year		250,571	2,778

Perkins

PARENT COMPANY

Income statement

SEK thousands	Note	1999	1998
Net turnover	1	114,166	73,817
Cost of goods sold	2, 14	-24,121	-18,190
Gross income		**90,045**	**55,627**
Selling expenses	2, 14	-32,347	-23,807
Administrative expenses	2, 14	-15,386	-8,982
Research and development costs	2, 14	-21,968	-6,651
Other operating revenues	3	2,818	2,092
Other operating expenses	4	-887	-2,970
Operating income		**22,275**	**15,309**
Result from financial items	5	-1,126	-787
Income after financial items		**21,149**	**14,522**
Appropriations	9	-4,322	-6,120
Income before tax		**16,827**	**8,402**
Tax	6	-	-2,439
Net income for the year		**16,827**	**5,963**

Balance sheet

SEK thousands	Note	Dec 31, 1999	Dec 31, 1998
ASSETS			
Fixed assets			
Intangible assets			
Capitalized R&D expenses	2	-	53
Patents and other intellectual property	2	956	233
Tangible assets			
Buildings and land	2	41,892	33,121
Plant and machinery	2	22,970	12,485
Equipment, fixtures and fittings	2	5,167	4,003
Ongoing new facility and advance payment to suppliers		4,879	3,016
Financial assets			
Shares in subsidiaries	7	8,951	8,861
Other financial assets		5,603	-
Other long-term receivables		608	570
Total fixed assets		**91,026**	**62,342**
Current assets			
Inventories			
Raw materials and consumables		6,926	3,093
Finished products and goods for resale		2,438	1,885
Current receivables			
Accounts receivable		14,595	8,919
Receivables from subsidiaries		14,917	9,571
Other current receivables		4,262	3,203
Prepaid expenses and accrued revenues		907	307
Cash and bank deposits		245,775	9
Total current assets		**289,820**	**26,987**
TOTAL ASSETS		**380,846**	**89,329**

Balance sheet cont.

SEK thousands	Note	Dec 31, 1999	Dec 31, 1998
LIABILITIES AND SHAREHOLDERS' EQUITY			
Shareholders' equity	8		
Restricted shareholders' equity			
Share capital		1,596	1,187
Statutory reserve		20	20
Share premium reserve		285,160	25,512
Unrestricted shareholders' equity			
Retained earnings		11,475	5,571
Net income for the year		16,827	5,963
Total shareholders' equity		**315,078**	**38,253**
Untaxed reserves	9	**13,695**	**9,373**
Long-term liabilities	10, 12		
Overdraft facility utilized		-	17,951
Loans from STU & NUTEK		-	1,601
Liabilities to credit institutions		26,691	
Total long-term liabilities		**26,691**	**19,552**
Current liabilities			
Liabilities to credit institutions	11, 12	6,023	4,500
Accounts payable		11,186	8,375
Liabilities to subsidiaries		1,543	1,730
Tax liabilities		-	2,354
Other current liabilities		1,208	441
Accrued expenses and prepaid revenues		5,422	4,751
Total current liabilities		**25,382**	**22,151**
TOTAL LIABILITIES AND SHAREHOLDERS' EQUITY		**380.846**	**89,329**
Collateral to secure own liabilities	12	55,100	25,100
Contingent liabilities		-	-

Cash flow analysis

SEK thousands	Note	1999	1998
Operating activities			
Income after financial items		21,149	14,521
Adjustments for items not included in the cash flow, etc.	13	5,226	2,035
Tax paid		-3,389	-2,485
Cash flow from operating activities before changes in working capital		**22,986**	**14,071**
Increase(-)/Decrease(+) in inventories		-4,387	-3,326
Increase(-)/Decrease(+) in trade receivables		-10,884	-5,248
Increase(+)/Decrease(-) in trade payables		3,976	8,191
Cash flow from operating activities		**11,691**	**13,688**
Investing activities			
Acquisition of subsidiaries		-90	-8,540
Acquisition of intangible fixed assets		-823	-
Acquisition of tangible fixed assets		-27,674	-40,752
Acquisition of financial assets		-5,695	-
Cash flow from investing activities		**-34,282**	**-49,292**
Financing activities			
Proceeds from issuance of share capital		259,648	-
Proceeds from borrowings		26,660	18,000
Repayment of borrowings		-17,951	-
Cash flow from financing activities		**268,357**	**18,000**
Cash flow for the year		**245,766**	**-17,604**
Cash and bank deposits at beginning of year		9	17,613
Cash and bank deposits at end of year		245,775	9

ACCOUNTING AND VALUATION PRINCIPLES

PRINCIPLES OF ACCOUNTING

The company's accounting and valuation principles are in accordance with the recommendations and pronouncements of the Swedish Financial Accounting Standards Council. Unless otherwise stated the principles are unchanged from the previous year.

The consolidated accounts include the Parent Company, Q-Med AB (publ), and the subsidiaries in which the Parent Company held shares carrying more than half of the voting rights at year-end. The consolidated accounts have been prepared in accordance with the Swedish Financial Accounting Standards Council's recommendation pertaining to consolidated accounting and the acquisition accounting method has been applied.

Translation of foreign subsidiaries' financial statements

The balance sheets and income statements of foreign subsidiaries are translated in accordance with the current method. Accordingly, assets and liabilities of foreign subsidiaries are translated at year-end exchange rates. All income statement items are translated at the average exchange rate for the year. Translation differences do not affect Group results and are transferred directly to shareholders' equity.

The following exchange rates have been used in the annual accounts:

	Average exchange rate		Year-end exchange rate	
Currency	1999	1998	Dec 31, 1999	Dec 31, 1998
AUD	5.335	5.008	5.563	4.983
CAD	5.564	5.367	5.873	5.208
DEM	4.506	4.525	4.378	4.814
FRF	1.343	1.350	1.305	1.436
GBP	13.370	13.166	13.795	13.425
ITL	0.00455	0.00458	0.00442	0.00485
NZD	4.377	4.273	4.438	4.200
USD	8.264	7.950	8.525	8.005

Deferred tax

When preparing the consolidated balance sheet, untaxed reserves are divided into a portion that is shown as a deferred tax liability (28%) under the heading Provisions and a portion that is reported among restricted reserves under Shareholders' equity. Appropriations involving changes in untaxed reserves are eliminated in the consolidated income statement. The tax portion of these changes is reported in the tax expense for the year in the consolidated income statement, while the equity portion is included in Net income for the year.

PRINCIPLES OF VALUATION

Assets and liabilities have been valued at their acquisition value unless otherwise stated below.

Receivables and liabilities in foreign currency

Receivables and liabilities in foreign currency have been valued at year-end exchange rates. Exchange gains and losses on the business operations' receivables and liabilities are reported in the operating income. Forward covered receivables and liabilities have been valued at the current forward rate. The currencies of greatest importance for Q-Med are the euro and the American dollar. The majority of Q-Med's sales are to Italy and Brazil. Payment is made there in French francs and American dollars, respectively. Purchases in foreign currency are matched through currency accounts against the inflow, although these purchases are relatively marginal. Forward cover of the three most important currencies is done regularly for a term of approximately 6 months. The Parent Company sells to the subsidiaries in their own local currency only. Of the Parent Company's exposure 58% (40) of the turnover was covered during 1999.

Inventories

Inventories are valued in accordance with the lowest-value principle, meaning the lower of acquisition cost and net sales value. The FIFO (first in/first out) principle is applied in calculating acquisition cost.

Fixed assets

Fixed assets are stated at acquisition cost after deduction for accumulated depreciation according to plan. Depreciation according to plan is based on the acquisition values of the assets and their estimated economic life. The goodwill which arose when the medical development company Qvestor was purchased is amortized at a rate of 10% annually, due to the fact that the company's main assets consist of patents that have a life length exceeding 10 years. Other goodwill is amortized at a rate of 20% annually. Patents and other intellectual property are written off at a rate of 20% annually, machinery at 10 - 20%, inventories and installations at 10 - 30% and buildings at 4%. Expenses for research and development are written off continually, though certain development costs have been activated earlier. These capitalized development costs are written off at a rate of 20% annually and were completely written off during the first half of 1999. A lump sum of USD 100,000 which was paid in settlement of a legal dispute, is recorded as an intangible asset. Amortization according to plan will be begun when Q-Med reports sales of RESTYLANE in the USA.

NOTES

Note 1. Net turnover

	Group		Parent Company	
SEK thousands	1999	1998	1999	1998
Nordic countries	25,585	18,305	25,600	18,305
Rest of Europe	74,180	44,996	52,389	36,662
North and South America	29,545	17,040	26,162	16,487
Rest of world	14,348	3,701	10,015	2,363
Total	**143,658**	**84,042**	**114,166**	**73,817**

The figures for 1998 are corrected so that they are in accordance with 1999's principle of recording exchange gains in the item Other operating revenues, not in Net turnover.

Note 2. Fixed assets

	Group		Parent Company	
SEK thousands	1999	1998	1999	1998
Intangible assets				
Capitalized R&D expenses				
Opening balance acquisition values	800	800	800	800
Purchases during the period	-	-	-	-
Sales / disposals	-	-	-	-
Closing balance accumulated acquisition values	800	800	800	800
Opening balance amortization	-747	-587	-747	-587
Amortization during the period	-53	-160	-53	-160
Sales / disposals	-	-	-	-
Closing balance accumulated amortization	-800	-747	-800	-747
Closing balance planned residual value	**-**	**53**	**-**	**53**
Patents and other intellectual property				
Opening balance acquisition values	500	530	500	500
Purchases during the period	854	-	823	-
Sales / disposals	-	-30	-	-
Closing balance accumulated acquisition values	1,354	500	1,323	500
Opening balance amortization	-267	-174	-267	-167
Amortization during the period	-100	-101	-100	-100
Sales / disposals	-	8	-	-
Closing balance accumulated amortization	-367	-267	-367	-267
Closing balance planned residual value	**987**	**233**	**956**	**233**
Goodwill				
Opening balance acquisition values	6,870	-	-	-
Purchases during the period	-	6,870	-	-
Sales / disposals	-	-	-	-
Closing balance accumulated acquisition values	6,870	6,870	-	-
Opening balance amortization	-696	-	-	-
Amortization during the period	-848	-696	-	-
Sales / disposals	-	-	-	-
Closing balance accumulated amortization	1,544	-696	-	-
Closing balance planned residual value	**5,326**	**6,174**	**-**	**-**

Note 2. Fixed assets cont.

	Group		Parent Company	
SEK thousands	1999	1998	1999	1998
Tangible assets				
Buildings and land				
Opening balance acquisition values	34,016	9,883	34,016	9,883
Purchases during the period	10,080	24,133	10,080	24,133
Sales / disposals	-	-	-	-
Closing balance accumulated acquisition values	44,096	34,016	44,096	34,016
Opening balance depreciation	-895	-407	-895	-407
Depreciation during the period	-1,309	-488	-1,309	-488
Sales / disposals	-	-	-	-
Closing balance accumulated depreciation	-2,204	-895	-2,204	-895
Closing balance planned residual value	**41,892**	**33,121**	**41,892**	**33,121**
Plant and machinery				
Opening balance acquisition values	13,686	2,329	13,686	2,329
Purchases during the period	13,115	11,515	13,115	11,515
Sales / disposals	-505	-158	-505	-158
Closing balance accumulated acquisition values	26,296	13,686	26,296	13,686
Opening balance depreciation	-1,201	-696	-1,201	-696
Depreciation during the period	-2,429	-529	-2,429	-529
Sales / disposals	304	24	304	24
Closing balance accumulated depreciation	-3,326	-1,201	-3,326	-1,201
Closing balance planned residual value	**22,970**	**12,485**	**22,970**	**12,485**
Equipment, fixtures and fittings				
Opening balance acquisition values	6,259	3,550	5,405	3,185
Purchases during the period	3,358	2,709	2,617	2,220
Sales / disposals	-443	-	-406	-
Closing balance accumulated acquisition values	9,174	6,259	7,616	5,405
Opening balance depreciation	-1,614	-735	-1,403	-692
Depreciation during the period	-1,636	-879	-1,310	-711
Sales / disposals	294	-	264	-
Closing balance accumulated depreciation	-2,956	-1,614	-2,449	-1,403
Closing balance planned residual value	**6,218**	**4,645**	**5,167**	**4,002**

Depreciation and amortization in the income statement has been divided up per function as follows:

	Group		Parent Company	
SEK thousands	1999	1998	1999	1998
Cost of goods sold	3,028	962	3,028	962
Selling expenses	805	376	465	197
Administrative expenses	560	342	560	342
Research and development costs	2,340	1,184	1,492	487
Total	**6,733**	**2,864**	**5,545**	**1,988**

The amortization of goodwill with regard to the acquisition of subsidiaries is recorded as a research and development cost. Previously this was recorded in the row Other operating expenses. 1998's figures for comparison have been corrected to be in accordance with 1999's principle.

Properties, Parent Company

	Taxable value	
SEK thousands	Dec 31, 1999	Dec 31, 1998
Buildings	10,427	3,276
Land	1,891	1,034
Total	**12,318**	**4,310**

Note 3. Other operating revenues

	Group		Parent Company	
SEK thousands	1999	1998	1999	1998
Write-down of loan from STU & NUTEK	2,166	-	2,166	-
Profit, sale of machine	275	-	275	-
Royalty	-	153	-	153
Exchange gains on accounts receivable and payable	184	1,113	184	1,113
Other	316	858	193	826
Total	**2,941**	**2,124**	**2,818**	**2,092**

1998's figures are corrected to be in accordance with 1999's principle of recording exchange gains in the item Other operating revenues, not in Net turnover.

Note 4. Other operating expenses

	Group		Parent Company	
SEK thousands	1999	1998	1999	1998
Building repairs	-	2,321	-	2,321
Exchange losses on accounts receivable and payable	759	191	887	191
Loss, sale of machine	-	458	-	458
Total	**759**	**2,970**	**887**	**2,970**

1998's figures are corrected to be in accordance with 1999's principle of recording exchange losses in the item Other operating expenses, not divided up per cost function.

Note 5. Result from financial items

	Group		Parent Company	
SEK thousands	1999	1998	1999	1998
Write-down of shares in subsidiaries	-	-	-	-178
Interest income	674	411	653	363
Interest expenses	-1,610	-949	-1,609	-938
Exchange losses	-170	-34	-170	-34
Total	**-1,106**	**-572**	**-1,126**	**-787**

Note 6. Taxes

	Group	
SEK thousands	1999	1998
Current tax	264	2,621
Deferred tax	1,172	1,563
Total	**1,436**	**4,184**

The current tax amounts to nil in the Parent Company due to tax relief for costs in connection with the new share issue on December 6, 1999. The deficit for tax purposes which is left after this year's tax relief amounts to approximately SEK 15 million.

Note 7. Shares in subsidiaries

SEK thousands	Corp. reg. no.	Registered office	Number	Proportion of share capital, %	Par value / share	Book value
Qvestor AB (dormant)	556483-0254	Uppsala, Sweden	1,000	100	100 SEK	8,100
Spectra Lab i Uppsala AB (dormant)	556382-1387	Uppsala, Sweden	1,000	100	100 SEK	100
Q-MED S.a.r.l.	159302	Paris, France	500	100	100 FRF	64
Q-Med (UK) Ltd	3268714	London, UK	100	100	1 GBP	1
Q-Med GmbH	AB9726	Frankfurt, Germany	1	100	50,000 DEM	256
Q-Med (Sweden) Australia Pty Ltd	078717076	Sydney, Australia	1	100	1 AUD	0
Q-Med of Scandinavia, Inc. (dormant)	52-2084574	Wilmington, USA	1,000	100	25 USD	199
Q-Med, Inc.	1285218	Toronto, Canada	1,000	100	25 CAD	141
Q-Med Italia S.R.L.	8794/1999	Codogno, Italy	1	100	10,000 EUR	90
Total						**8,951**

During 1999 the establishment of a subsidiary in Brazil was begun.

Note 8. Shareholders' equity

At December 31, 1999 the share capital amounted to SEK 1,596,350, represented by 22,805,000 shares, each with a par value of SEK 0.07 and carrying one vote.

SEK thousands	Share capital	Restricted reserves	Unrestricted reserves	Total shareholders' equity
Group				
Balance sheet, December 31, 1998	1,187	32,330	5,561	39,078
Bonus share issue	59		-59	-
Options programme		2,050		2,050
New share issue	350	257,598		257,948
Shift from unrestricted to restricted shareholders' equity		3,111	-3,111	-
Translation difference		-3	88	85
Net income for the year			15,698	15,698
Balance sheet, December 31, 1999	**1,596**	**295,086**	**18,177**	**314,859**

SEK thousands	Share capital	Statutory reserve	Share premium reserve	Unrestricted reserves	Total shareholders' equity
Parent Company					
Balance sheet, December 31, 1998	1,187	20	25,512	11,534	38,253
Bonus share issue	59			-59	-
Options programme			2,050		2,050
New share issue	350		257,598		257,948
Net income for the year				16,827	16,827
Balance sheet, December 31, 1999	**1,596**	**20**	**285,160**	**28,302**	**315,078**

In December 1999 a new share issue of SEK 290.0 million was carried out. Issue expenses have not been charged against income for the year, but have been offset by an issue premium before being transferred to restricted reserves. After issue expenses, the share issue brought in SEK 257.9 million net to the company.

Note 9. Untaxed reserves, Parent Company

SEK thousands	Dec 31, 1999	Change	Dec 31, 1998
Tax deferment reserves			
Assessment of tax 1995	-	-10	10
Assessment of tax 1996	150	-	150
Assessment of tax 1997	295	-	295
Assessment of tax 1998 (May 1, 1996 - Apr 30, 1997)	464	-	464
Assessment of tax 1998 (May 1, 1997 - Dec 31, 1997)	1,489	-	1,489
Assessment of tax 1999	2,180	-	2,180
Assessment of tax 2000	-	-	-
Additional depreciation			
Patents and other intellectual property, plant and machinery, equipment, fixtures and fittings	9,117	4,381	4,736
Foreign exchange reserve	-	-49	49
Total	**13,695**	**4,322**	**9,373**

The above sum includes 28% deferred tax, corresponding to SEK 3,835 thousand (2,624).
The year's change in untaxed reserves, SEK 4,322 million (6,120), is recorded in the Parent Company's income statement in the row Appropriations.

Note 10. Long-term liabilities

	Group		Parent Company	
SEK thousands	Dec 31, 1999	Dec 31, 1998	Dec 31, 1999	Dec 31, 1998
Interest-bearing	26,922	19,151	26,691	19,151
Interest-free	-	401	-	401
Total	**26,922**	**19,552**	**26,691**	**19,552**

The loan from STU & NUTEK was completely written off during 1999, see note 3, Other operating revenues.
All long-term liabilities will be paid off within five years.

Note 11. Short-term liabilities to credit institution

Interest-bearing short-term liabilities amount to SEK 6,023 thousand, which corresponds to that part of the long-term liabilities which will be paid off during the year 2000.

Note 12. Collateral

	Group		Parent Company	
SEK thousands	Dec 31, 1999	Dec 31, 1998	Dec 31, 1999	Dec 31, 1998
Real estate mortgages	37,100	17,100	37,100	17,100
Chattel mortgages	18,000	8,000	18,000	8,000
Total	**55,100**	**25,100**	**55,100**	**25,100**

All collateral is liabilities to credit institutions to secure own commitments.
In addition, Q-Med has pledged to Bengt Ågerup the rights concerning the NASHA technology that were acquired from Bengt Ågerup as collateral for Q-Med's meeting of the commitments which were assumed upon the acquisition, such as the maintaining of patent registrations and alike.

Note 13. Cash flow analysis

	Group		Parent Company	
SEK thousands	1999	1998	1999	1998
Adjustment for items not included in the cash flow:				
Writing off and down of assets	6,733	2,864	5,545	1,988
Non-realized exchange rate differences	27	21	-319	47
Other allocations	-254	2,082	-	-
Total	**6,506**	**4,967**	**5,226**	**2,035**
Acquisition of subsidiaries and other business units:				
Acquired assets and liabilities:				
Intangible assets	-	60	-	-
Tangible assets	-	224	-	-
Inventories	-	25	-	-
Current receivables	-	1,848	-	-
Cash and bank deposits	90	1,378	-	-
Total assets	**90**	**3,535**	**-**	**-**
Allocations	-	120	-	-
Short-term liabilities	-	1,711	-	-
Total allocations and liabilities	**-**	**1,831**	**-**	**-**
Purchase sum paid	90	8,540	90	8,540
Cash and bank deposits in the acquired subsidiaries	-90	-1,378	-	-
Effect on cash and bank deposits	**-**	**7,162**	**90**	**8,540**

The Parent Company had a non-utilized bank overdraft facility amounting to SEK 20 million at December 31, 1999.

Note 14. Average number of employees; wages, salaries and other remuneration

Average number of employees

	Total		of whom, women	
	1999	1998	1999	1998
Parent Company				
Uppsala, Sweden	71	41	43	23
Subsidiaries				
France	8	4	8	4
Australia / New Zealand	5	4	3	2
United Kingdom	4	2	2	1
Germany	2	1	1	-
USA / Canada	5	3	3	2
Total, Group	**95**	**55**	**60**	**32**

Note 14. Average number of employees; wages, salaries and other remuneration cont.

Wages, salaries, other remuneration and social security expenses

	Wages, salaries and other remuneration		Social security expenses	
SEK thousands	1999	1998	1999	1998
Parent Company	21,609	11,254	10,795	4,555
- including pension costs of			(3,079)	(923)
Subsidiaries	10,382	5,456	1,714	959
- including pension costs of			(257)	(678)
Total, Group	**33,991**	**16,710**	**12,509**	**5,514**

Wages, salaries and other remuneration divided up per country and among Board members/CEO/Deputy CEO and other employees

	Board/CEO/Dep. CEO		Other employees	
SEK thousands	1999	1998	1999	1998
Sweden	1,254	1,020	20,355	10,234
France	188	121	2,200	1,180
Australia / New Zealand	526	607	1,375	557
United Kingdom	473	326	1,032	304
Germany	1,829	1,081	293	77
USA / Canada	1,782	1,137	684	66
Total, Group	**6,052**	**4,292**	**25,939**	**12,418**

For the period 98/99 SEK 60,000 (60,000) has been paid out to the Board of the Parent Company, including no fee to the Chairman of the Board, Robert Wikholm. For the period 99/00 fees of SEK 200,000 will be paid out to the Board during spring 2000, including SEK 20,000 to the Chairman of the Board. The Chairman of the Board is the company's legal representative and has received a normal lawyer's fee for legal services. Other members of the Board have not received any other remuneration.

For the period April - December SEK 721,200 has been paid in salary and pension premiums to the President and CEO Per Olof Wallström. To the Deputy CEO Bengt Ågerup SEK 240,000 was paid for the period January - March in his capacity as President, and during the period April - December SEK 450,000 in his capacity as Deputy CEO. The period of notice on both sides is six months for both the CEO and the Deputy CEO. There are no pension commitments to the Board and Deputy CEO, while for the CEO pension insurance premiums are paid.

For other senior managers in the Group normal conditions apply to pension and period of notice.

Auditors' fees

	Group	Parent Company
SEK thousands	1999	1999
Audit fee	448	233
Consultant's fee	361	158
Total	**809**	**391**

Stockholm, Sweden, March 9, 2000

Robert Wikholm
Chairman of the Board

Tomas Billing

Ugo Grondelli

Anders Milton

Björn Odlander

Bengt Ågerup

Per Olof Wallström
President and Chief Executive Officer

AUDITORS' REPORT

To the General Meeting of the shareholders of Q-Med AB (publ), registered number 556258-6882.

We have audited the annual accounts, the consolidated accounts, the accounting records and the administration of the Board of Directors and the Chief Executive Officer of Q-Med AB (publ) for the year 1999. These accounts and the administration of the Company are the responsibility of the Board of Directors and the Chief Executive Officer. Our responsibility is to express an opinion on the annual accounts, the consolidated accounts and the administration based on our audit.

We conducted our audit in accordance with Generally Accepted Auditing Standards in Sweden. Those Standards require that we plan and perform the audit to obtain reasonable assurance that the annual accounts and the consolidated accounts are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the accounts. An audit also includes assessing the accounting principles used and their application by the Board of Directors and the Chief Executive Officer, as well as evaluating the overall presentation of information in the annual accounts and the consolidated accounts. As a basis for our opinion concerning discharge from liability, we examined significant decisions, actions taken and circumstances of the Company in order to be able to determine the liability, if any, to the Company of any Board member or the Chief Executive Officer. We also examined whether any Board member or the Chief Executive Officer has, in any other way, acted in contravention of the Companies Act, the Annual Accounts Act or the Articles of Association. We believe that our audit provides a reasonable basis for our opinion set out below.

The annual accounts and the consolidated accounts have been prepared in accordance with the Annual Accounts Act and, thereby, give a true and fair view of the Company's and the Group's financial position and results of operations in accordance with Generally Accepted Accounting Principles in Sweden.

We recommend to the General Meeting of shareholders that the income statements and balance sheets of the Parent Company and the Group be adopted, that the profit for the Parent Company be dealt with in accordance with the proposal in the Administration Report and that the members of the Board of Directors and the Chief Executive Officer be discharged from liability for the financial year.

Uppsala, Sweden, March 10, 2000

Hans Karlsson
Authorized Public Accountant

Lennart Jakobsson
Authorized Public Accountant

5-YEAR SUMMARY

INCOME STATEMENTS

SEK thousands	1999	1998	Pro forma 1997	May 1, 1996- Apr 30, 1997	May 1, 1995- Apr 30, 1996
Net turnover	143,658	84,042	46,035	26,555	16,094
Operating income before depreciation	24,973	15,316	7,265	4,277	2,023
Operating income after depreciation	18,240	12,452	6,040	3,181	1,559
Income after financial items	17,134	11,880	5,949	2,574	1,217
Net income for the year	15,698	7,696	3,631	1,832	884

Note: The figures for 1998 are corrected to be in accordance with 1999's principle of not recording exchange gains in the turnover figure but in the item Other operating revenues. The effects in previous years' figures are not tangible.

BALANCE SHEETS

SEK thousands	Dec 31, 1999	Dec 31, 1998	Dec 31, 1997	Apr 30, 1997	Apr 30, 1996
ASSETS					
Fixed assets					
Intangible assets	6,313	6,460	569	742	480
Tangible assets	75,959	53,267	13,924	9,401	4,979
Financial assets	6,366	643	585	706	369
Current assets					
Inventories	9,718	5,355	1,975	818	184
Accounts receivable	26,026	13,938	11,027	8,847	2,577
Other current receivables	6,040	4,523	1,861	1,177	1,180
Cash and bank deposits	250,571	2,778	18,845	448	9
TOTAL ASSETS	**380,993**	**86,964**	**48,786**	**22,139**	**9,778**
LIABILITIES AND SHAREHOLDERS' EQUITY					
Shareholders' equity	314,859	39,078	31,407	3,346	1,483
Provisions	5,232	4,314	550	393	161
Long-term liabilities					
Interest-bearing long-term liabilities	26,922	19,151	5,700	9,350	4,507
Interest-free long-term liabilities	-	401	353	300	300
Current liabilities					
Interest-bearing current liabilities	6,023	4,500	-	-	-
Accounts payable	12,255	9,818	3,104	2,387	1,120
Other interest-free current liabilities	15,702	9,702	7,672	6,363	2,207
TOTAL LIABILITIES AND SHAREHOLDERS' EQUITY	**380,993**	**86,964**	**48,786**	**22,139**	**9,778**

CASH FLOW ANALYSES

SEK thousands	1999	1998	Pro forma 1997	May 1, 1996- Apr 30, 1997	May 1, 1995- Apr 30, 1996
Cash flow from operating activities	14,134	14,082	1,076	1,450	1,300
Cash flow from investing activities	-34,970	-48,100	-6,582	-6,117	-4,595
Cash flow from financing activities	268,629	17,951	23,070	5,106	3,301
Cash flow for the year	247,793	-16,067	17,564	439	6
Cash and bank deposits at beginning of year	2,778	18,845	1,281	9	3
Cash and bank deposits at end of year	250,571	2,778	18,845	448	9

Note: The figures in the cash flow analyses for the years 1997 and earlier have not been recalculated according to the Swedish Financial Accounting Standards Council's recommendation no.7. The differences are not tangible.
Note: Before 1997 no Group existed. The figures for earlier periods are calculated on the basis of the Parent Company's annual accounts.

KEY RATIOS AND DEFINITIONS

KEY RATIOS

	1999	1998	Pro forma 1997	May 1, 1996- Apr 30, 1997	May 1, 1995- Apr 30, 1996
Margins					
Gross margin, %	84.3	78.3	79.9	77.9	na
Operating margin before depreciation and amortization, %	17.4	18.2	16.0	16.4	12.6
Operating margin, %	12.7	14.8	13.3	12.2	9.7
Profit margin, %	10.9	9.2	8.0	7.0	5.5
Return ratios					
Return on capital employed, %	9.2	25.8	27.1	34.5	39.5
Return on shareholders' equity, %	8.9	21.8	21.7	75.8	84.8
Working and capital intensity					
Capital turnover ratio, times	0.7	1.7	1.9	2.8	3.9
Net turnover per employee, SEK thousands	1,512	1,528	1,894	1,858	2,299
Average number of employees	95	55	24	14	7
Financial ratios					
Debt/equity ratio, times	0.1	0.6	0.2	2.8	3.0
Equity/assets ratio, %	82.6	44.9	64.4	15.1	15.2
Interest-coverage ratio, times	10.6	13.1	11.8	5.0	4.0
Share data					
Average number of outstanding shares	18,221,667	17,805,000	16,636,250	15,000,000	15,000,000
Number of shares outstanding at year-end	22,805,000	17,805,000	17,805,000	15,000,000	15,000,000
Earnings per share, SEK	0.86	0.43	0.22	0.12	0.06
Earnings per share after full dilution, SEK	0.77	0.39	0.21	0.12	0.06
Operating cash flow per share, SEK	-0.53	-1.20	-0.19	-0.22	-0.17
Shareholders' equity per share, SEK	13.81	2.19	1.76	0.22	0.10
Shareholders' equity per share after full dilution, SEK	12.50	1.97	1.61	0.22	0.10
Share price at year-end, SEK	67.00	na	na	na	na
P/e ratio	78	na	na	na	na

DEFINITIONS

Gross margin Net turnover minus cost of goods sold as a percentage of the net turnover for the period.

Operating margin before depreciation and amortization Operating income before depreciation and amortization as a percentage of the net turnover for the period.

Operating margin Operating income after depreciation and amortization as a percentage of the net turnover for the period.

Profit margin The income for the period as a percentage of the net turnover for the period.

Return on capital employed Income after financial items plus financial expenses as a percentage of the average capital employed for the period. Financial expenses include interest expenses, exchange rate differences on loans and other financial expenses. Capital employed is defined as total assets less interest-free liabilities including provisions.

Return on shareholders' equity The income for the period as a percentage of the average shareholders' equity for the period.

Capital turnover ratio The net turnover for the period in relation to the average capital employed for the period.

Net turnover per employee The net turnover for the period in relation to the average number of full-time employees for the period.

Debt/equity ratio Interest-bearing liabilities in relation to shareholders' equity.

Equity/assets ratio Shareholders' equity as a percentage of total assets.

Interest-coverage ratio Income after financial items plus financial expenses in relation to financial expenses.

Share data Previous years' figures have been recalculated taking into account bonus share issues, new share issues and splits carried out since the founding of the company.

Earnings per share The earnings for the period in relation to the average number of outstanding shares for the period.

Earnings per share after full dilution The earnings for the period in relation to the average number of outstanding shares for the period, taking outstanding subscription options into account.

Operating cash flow per share The cash flow for the period from the current year's operations, excluding interest and taxes, with the addition of investments in tangible fixed assets, in relation to the average number of outstanding shares for the period.

Shareholders' equity per share Shareholders' equity in relation to the number of shares outstanding at year-end.

Shareholders' equity per share after full dilution Shareholders' equity in relation to the number of shares outstanding at year-end, taking outstanding subscription options into account.

P/e ratio The share price at year-end divided by earnings per share.

GENERAL MEETINGS OF THE SHAREHOLDERS

GENERAL MEETINGS OF THE SHAREHOLDERS 1999

At the Annual General Meeting of the shareholders of Q-Med AB (publ) held on May 4 it was decided to adopt new Articles of Association and to carry out a bonus share issue and a split. The Board was authorized to approve a new share issue. Tomas Billing, Anders Milton, Björn Odlander, Robert Wikholm and Bengt Ågerup were re-elected as members of the Board while Kurt Ågerup had declined re-election. Ugo Grondelli was elected as a new member of the Board. Lennart Jakobsson and Hans Karlsson, both authorized public accountants from KPMG, were re-elected as the company's auditors. Furthermore, it was decided that no dividend would be paid out for the financial year 1998.

At the Extraordinary General Meeting of the shareholders on August 26 it was decided to raise subordinated loans through the issue of debentures involving separable options to subscribe for 350,000 new shares. The right to subscribe was reserved for employees at Q-Med and its subsidiaries, as well as the wholly owned subsidiary Qvestor AB.

ANNUAL GENERAL MEETING 2000

The Annual General Meeting of Q-Med AB (publ) will be held on Wednesday May 10, 2000 at 5.30 p.m. at Eklundshof, Uppsala. Shareholders who wish to attend the Annual General Meeting should be entered in the register of shareholders maintained by VPC AB (Swedish Securities Register Centre) on Friday April 28, 2000. Furthermore, Q-Med would like to be notified of shareholders' intention to attend no later than Friday May 5, 2000. This can be done through Kristin Ermanbriks, either in writing to Q-Med AB (publ), Seminariegatan 21, 752 28 Uppsala, Sweden, by telephone (+46 18 474 90 00), by fax (+46 18 474 90 97) or by e-mail to anmalan@q-med.com. The shareholder should give his name, personal identity number or corporate identity number, address, telephone number and number of shares. For shareholders who are represented by another party, a proxy should be sent together with the notification. Any party representing a legal entity must produce a copy of the certificate of incorporation or equivalent authorization documents showing the authorized signatory for the company.

In order to be entitled to attend the Annual General Meeting, shareholders whose shares are registered in the names of nominees, either through a bank or some other nominee, must, through the nominee, have their shares registered in their own names in good time before Friday April 28, 2000.

Shareholders who are entered in the register of shareholders or on a list in accordance with chapter 3 § 12 of the Companies Act are entitled to a dividend. The Board proposes no dividend for the financial year 1999. Therefore no record day is proposed either.

FINANCIAL INFORMATION

During the coming year Q-Med will publish the following reports:

Report for the first three months	April 14, 2000
Report for the first six months	August 23, 2000
Report for the first nine months	October 26, 2000
Report on operations 2000	February 2001

The reports are available on Q-Med´s home page www.q-med.com as of these dates.

Anna Ahlberg

For further information on Q-Med, contact Anna Ahlberg, Director of Investor Relations, tel. +46 18 474 90 15 (direct line), +46 18 474 90 00 (switchboard) or via e-mail, info@q-med.com.

BOARD OF DIRECTORS

ROBERT WIKHOLM
Born 1953. Lawyer and partner, Advokatfirman Vinge KB, Board member and Chairman since 1997.
Other Board of Director assignments: -
Shareholding in Q-Med: 12,600 shares.

BENGT ÅGERUP
Born 1943. Q-Med's founder, President from 1995 to April 1, 1999. Deputy Chief Executive Officer and Vice President of Research and Development, member of the Board since 1987.
Other Board of Director assignments: Member of the Board of Ixion and Medical Innovation Centre, Karolinska Institute.
Shareholding in Q-Med: 13,900,000 shares.


Robert Wikholm


Bengt Ågerup


Tomas Billing


Ugo Grondelli


Anders Milton


Björn Odlander

TOMAS BILLING
Born 1963. President and Chief Executive Officer, Nordstjernan AB, Board member since 1997.
Other Board of Director assignments: Chairman of Karolin Machine Tools AB, Deputy Chairman of NCC AB.
Shareholding in Q-Med: 154,500 shares.

UGO GRONDELLI
Born 1945. Director, member of the Board since 1999.
Other Board of Director assignments: Member of the Board of Jostra AG and Dulevo International S.p.A.
Shareholding in Q-Med: -

ANDERS MILTON
Born 1947. Secretary General, Swedish Medical Association, Board member since 1997.
Other Board of Director assignments: Chairman of SACO (Swedish Confederation of Professional Associations) and the World Medical Association, Deputy Chairman of SalusAnsvar AB. Board member of the National Swedish Board of Health and Welfare, Maud and Birger Gustafsson's foundations and of the steering group for cooperation between the European medical associations and WHO's regional headquarters.
Shareholding in Q-Med: 157,500 shares.

BJÖRN ODLANDER
Born 1958. President, Odlander, Fredriksson & Co, Board member since 1997.
Other Board of Director assignments: Chairman of HealthCap AB. Board member of Biostratum, Inc., Medicarb AB, Melacure AB, Nicox S.A., Odlander, Fredrikson & Co AB, Personal Chemistry AB and Pyrosequencing AB.
Shareholding in Q-Med: -

SENIOR MANAGEMENT AND AUDITORS

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PER OLOF WALLSTRÖM
Born 1949. President and Chief Executive Officer, employed since 1999.
Shareholding in Q-Med: 100,300 shares and 150,000 subscription options.

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PETER HEIN
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ANNA ERIKSRUD
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Shareholding in Q-Med: -

BJÖRN FORSMAN
Born 1950. Vice President, Aesthetics Business Unit, employed since January 2000.
Shareholding in Q-Med: 1,000 shares.

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Born 1964. Director of Clinical Research and of the Orthopedics Business Unit, employed since 1999.
Shareholding in Q-Med: 500 shares and 15,000 subscription options.

GUNILLA LUNDMARK
Born 1963. Director of Quality Assurance, employed since February 2000.
Shareholding in Q-Med: 500 shares.

Shareholdings include those of spouse, children and closely related companies
See page 9 for information on options


Per Olof Wallström


Bengt Ågerup


Peter Hein


Anna Eriksrud


Björn Forsman


Jonas Lindgren


Gunilla Lundmark

Subsidiaries

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HANS GERIDANT
Managing Director, Q-Med GmbH, Germany, employed since 1997.

MARTIN INGMAN
Managing Director, Q-Med (UK) Ltd., UK, employed since 1998.

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UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	5,827,937
(45)	ISSUED	:	October 27, 1998
(75)	INVENTOR	:	Bengt Ågerup
(73)	PATENT OWNER	:	Q-Med AB
(95)	PRODUCT	:	RESTYLANE® (Injectable Gel)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 5,827,937 based upon the regulatory review of the product RESTYLANE® (Injectable Gel) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 879 days

from July 17, 2015, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the United States Patent and Trademark Office to be affixed this 4th day of October 2007.

Jon W. Dudas
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Restylane SubQ, a Non-Animal Stabilized Hyaluronic Acid Gel for Soft Tissue Augmentation of the Mid- and Lower Face

Alexis Verpaele, MD; and Anders Strand, MD

Dr. Verpaele is Assistant Clinical Professor, Department of Plastic Surgery, Ghent University Hospital and Director, Coupure Center for Plastic Surgery, Ghent, Belgium. Dr Strand is from Q-Med AB, Uppsala, Sweden.

For people requiring large volumes to shape facial contours, add volume to a sunken midface, or correct asymmetry, the options today are limited. Fat injections for adding volume, solid implants for cheeks and chin enhancement, face lift and injectable permanent or semi-permanent products are some of the alternatives used. With the trend towards less invasive and nonpermanent alternatives to plastic surgery, the use of injectable filler materials for facial rejuvenation and correction of soft-tissue defects is becoming increasingly popular. These materials provide volume expansion within the dermis, thereby smoothing out overlying facial wrinkles and enhancing facial contours. Ease of application, minimal procedural discomfort, and rapid patient recovery make injectable fillers well suited for outpatient use. Ideally, a filler material should be biocompatible, nontoxic, nonimmunogenic, and nonmigratory. Several biomaterials have been developed, such as bovine collagen, autologous and allogeneic human collagen, autologous fat, fibroblasts, and hyaluronic acid. However, although they are largely biocompatible, reabsorption and lack of sustained cosmetic effect are major drawbacks. Non-animal stabilized hyaluronic acid (NASHA) offers a longer-lasting aesthetic effect than bovine collagen or avian hyaluronic acid in facial soft-tissue augmentation, and a potentially lower risk of inflammatory reactions. Restylane SubQ is a new NASHA product indicated for deep subcutaneous or supraperiostal injection to replace volume loss in facial adipose tissues and create more defined facial contours.
(Aesthetic Surg J 2006;26(suppl):S10-S17.)

Statistics from the American Society for Aesthetic Plastic Surgery show that use of nonsurgical cosmetic procedures in the United States increased by 51% between 2003 and 2004.[1] As patients look toward less invasive and nonpermanent alternatives to plastic surgery, augmentation of facial features using injectable filler materials is fast becoming one of the most frequently performed aesthetic procedures. These viscoelastic materials provide volume expansion within the dermis and subcutaneous tissues, smoothing out facial wrinkles and folds and enhancing facial contours.

In addition to providing naturalistic volume expansion, the ideal filler material for soft tissue augmentation should be (1) nonimmunogenic and free of infectious agents; (2) easy to inject and allow rapid patient recovery; (3) natural looking and nonpalpable in situ; (4) nonmigratory; and (5) provide a long-lasting (but not permanent) and satisfying esthetic effect.

In recent years various new injectable fillers have become available, including synthetic products and autologous and heterologous natural materials.[2] These filler materials have their own specific merits and drawbacks.

Materials for Soft Tissue Volume Augmentation

Lipofilling, the technique of harvesting autologous fat at one site and injecting it at another site, is a well-established, safe, and natural way of altering face and body contours. Under optimal conditions, the procedure achieves good tissue augmentation and a durable cosmetic effect, with approximately 50% of the injected material persisting for at least 2 years.[3,4] However, there are limitations to this technique: the procedure is consuming of time and personnel, and moderate overcorrection is required at the initial treatment session, as subsequent fat resorption is unpredictable. Implantation of excessive amounts of fat can result in considerable edema and inflammation and also tends to promote local devascularization, which may cause cystic steatonecrosis. Moreover, fat must be injected in small deposits over large areas to ensure survival of the implanted fat. This results in a long recovery period for patients because of extensive swelling and bruising after treatment. Another disadvantage of lipofilling is that it requires a sterile setting and may involve pain at both the donor and injection sites, thus requiring use of locoregional anesthesia. Moreover, in some cases (most

notably, the patient with human immunodeficiency virus [HIV]–associated facial lipoatrophy), identification of an appropriate donor site may be complicated by a shortage of subcutaneous tissue.

For volume augmentation, permanent fillers such as polyacrylamide gels are also used. One such gel is Aquamid (Contura International A/S, Copenhagen, Denmark), in which the majority of the implant volume (97.5%) is composed of water (the remaining 2.5% is made of polyacrylamide). The cross-linked polyacrylamide forms a gel that does not contain any solid microparticles. Once injected, the gel becomes a stable part of the connective tissue. As with all permanent products, there is a risk of fibrosis and encapsulation of the implant. Complications can also manifest years after treatment, as changes in facial structure in the vicinity of the implant lead to loss of implant stability. Permanent injectables offer obvious benefits to patients and physicians in terms of convenience and cost. However, a prudent approach to their use is called for; reports in the literature indicate the possibility of long-term complications after injection of these materials.[5,6] It is important to realize that facial contours change over time—and permanent fillers may create an unnatural appearance as aging progresses. Any untoward consequence would be difficult or maybe even impossible to correct without surgical intervention. At least one European prospective multicenter study has been conducted that included 15 centers in 6 countries involving 247 patients. The study evaluated the safety and long-term cosmetic results of facial corrective plastic surgery.[7] In addition, an ongoing, retrospective, single-center European study is investigating the safety and long-term cosmetic results of Aquamid.

The semi-permanent filler Sculptra (Dermik Laboratories, Berwyn, PA) (also known as New Fill) is a pulverized crystalline form of poly-L-lactic acid (PLLA), a material known for its use in resorbable suture material, as well as for temporarily creating tissue barriers to separate different tissues in posttrauma and postsurgical healing situations. PLA acts as a volume expander for facial restructuring, and treatment involves several injections administered at monthly intervals. The effect of PLA is to create an increased skin thickness through fibroblast stimulation. Specifically, the PLA stimulates thickening of the collagen layer under the skin as the small PLA particles are encapsulated by fibrous tissue due to a foreign-body reaction. Thereafter, PLA particles are slowly resorbed and the remnants are removed by macrophages. The duration of the cosmetic effect is reported to vary from months to years. Sculptra is FDA-approved for patients with HIV-associated facial lipoatrophy. In the VEGA trial,[8] an open, noncomparative pilot study involving 50 patients, Sculptra significantly improved the restoration of facial thickness in HIV patients with facial loss of subcutaneous fat. Complications were mild, but palpable subcutaneous micronodules were observed in 22 (44%) patients, suggesting that this product is less suitable for superficial injection or for lip augmentation. In 6 of the 22 patients, these nodules resolved spontaneously after 2 years.

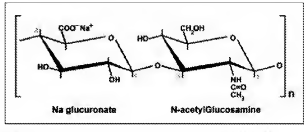

Figure 1. *Hyaluronic acid consists of repeating disaccharide units of sodium glucuronate and N-acetylglucosamine arranged in a linear chain.*

Hyaluronic Acid

In light of the limitations and disadvantages of these soft-tissue augmentation materials, another approach using a hyaluronic acid–based preparation has been explored.

Hyaluronic acid is a uniform, unbranched polysaccharide chain consisting of repeating disaccharide units of sodium glucuronate and N-acetylglucoamine (Figure 1). In solution, the polysaccharide chain bends and adopts an expanded coil-like structure. Crucially, hyaluronic acid has identical chemical composition in all species and tissues, making it nonimmunogenic and an ideal candidate for use as a filler material. Hyaluronic acid is found in all vertebrates, forming an essential component of the connective tissues, dermis, joints, interstitial membranes, and the vitreous body of the eye. The main function of hyaluronic acid in the extracellular matrix is stabilization of extracellular structures and formation of the matrix fluid in which elastic fibers and collagen are intermixed. Hyaluronic acid is strongly hydrophilic, conferring a natural hydrating function in the skin that contributes to its suppleness and turgor. While hyaluronic acid is abundant in neonates, production declines with age, causing dermal dehydration and signs of aging.

In view of its structural role in the tissues, protective effects on the cell membrane, and viscoelastic properties,

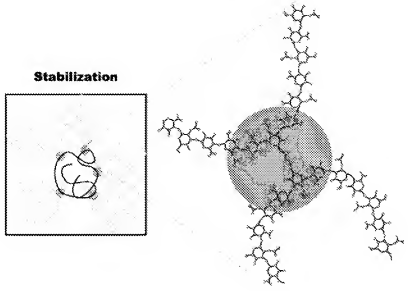

Figure 2. *Stabilization of hyaluronic acid in non-animal stabilized hyaluronic acid is achieved by cross-linking adjacent molecules, resulting in formation of a stable 3-dimensional hydrophilic matrix (gel).*

hyaluronic acid is an ideal substance to fill skin depressions and provides a natural look and structural stability.[4] Nearly 900,000 hyaluronic acid injections were performed in the United States in 2004, making it the most commonly used soft-tissue filler.[1] Corresponding statistics for the rest of the world are not available; however, because hyaluronic acid products have been available outside the United States for many years, it is likely that the total number of treatments performed worldwide would be appreciably higher.

Non-Animal Stabilized Hyaluronic Acid

In non-animal stabilized hyaluronic acid (NASHA), a biosynthetic hyaluronic acid product produced by the fermentation of streptococcal bacteria is used. These bacteria synthesize hyaluronic acid within the cell membrane, from which it is extruded into the extracellular medium. Harvesting is achieved by means of extraction and purification by alcohol precipitation. The use of NASHA reduces impurities and ensures the absence of immunologically active proteins and biologically active animal components, including viruses. No skin test is required prior to treatment with NASHA-based products.

The hyaluronic acid molecule must be modified to prolong its half-life in vivo.[2] Endogenous hyaluronic acid undergoes extremely rapid metabolic turnover, and has a tissue half-life ranging from 0.5 to a few days.[10,11] Hyaluronic acid can be modified through cross-linking of adjacent polymer chains to form a high-molecular-weight (~10 million Daltons) compound. In NASHA, the hyaluronic acid molecule has been stabilized through the introduction of minute amounts of cross-links between its constituent polysaccharide chains, resulting in the formation of an entangled matrix (gel) that is able to hold large volumes of water (Figure 2). The hyaluronic acid molecules in NASHA are loosely interlinked in a 3-dimensional gel structure that allows unhindered passage of nutrients, oxygen, and hormones, thereby enabling normal tissue function. The stabilization of the hyaluronic acid in NASHA results in prolongation of the tissue residence time to almost 12 months but does not reduce its biocompatibility. The compound remains resorbable, although it is degraded much more slowly than other hyaluronic acid preparations.

Metabolism of NASHA requires the degradation of the 3-dimensional hyaluronic acid gel matrix. The most probable means of degradation is by free radicals, which are present in very low concentrations in normal tissue. The NASHA gel is subject to isovolemic degradation, which enables the initial volume to be maintained throughout the degradation phase. When a stabilizing bridge disappears, water takes its place. The less concen-

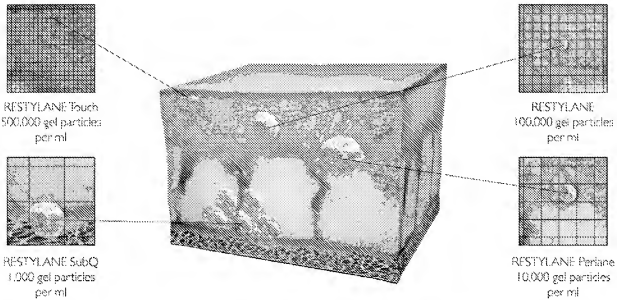

Figure 3. *The various non-animal stabilized hyaluronic acid preparations are designed to match the dermal structure at a specific level of injection.*

trated the NASHA gel becomes, the more water each molecule is able to bind. The result is that the same volume can be maintained with less implant material. Finally, the implant is fully degraded.

Currently Available NASHA-Based Products

NASHA has been used in a number of products for various clinical purposes, including urological (vesicoureteral reflux and stress urinary incontinence), orthopedic (knee and hip osteoarthritis), and facial aesthetic indications. All NASHA–based products are based on the same gel with the same high concentration of stabilized hyaluronic acid (20 mg/mL), and differ only in terms of the gel particle size. Five NASHA-based products are currently available, although in the United States only one of these products (Restylane) is approved by the FDA for instant aesthetic treatments:

- Restylane Touch: intended to fill out very thin and delicate wrinkle areas, primarily around the eyes and mouth (available in most countries outside the United States).
- Restylane: intended to fill out moderate wrinkles, smooth out scars and folds, and add volume to the lips (available worldwide).
- Restylane Perlane: intended to fill out deeper wrinkles and give volume to lips and skin indentations (available in most countries outside the United States).
- Restylane SubQ: intended for deep subcutaneous and/or supraperiostal injection to allow more extensive facial volume augmentation and structural support (available within Europe).
- Restylane Vital: for skin rejuvenation (available within Europe).

The various dermal layers of the skin are characterized by different tissue structures. If small implant particles are injected into deep tissue they could be lost; conversely, if larger particles are injected into the superficial dermis they may stretch or tear the much smaller matrix, producing uneven treatment results and possible trauma. For optimal lift and augmentation, the different NASHA products are designed to match the density of the tissues into which they are injected. Restylane Perlane (with its large gel particles) is intended for injection into the deep dermis, Restylane for injection into the middle dermis, and Restylane Touch (with the smallest gel particles) for injection into the superficial dermis[4] (Figure 3).

The duration of the cosmetic effects varies between individual patients, but is generally of the order of 6 to 12 months.

Some common injection-related reactions may occur after injection of the Restylane products. These reactions include erythema, swelling, pain, itching, and discoloration or tenderness at the implant site. Typically, resolution is spontaneous within a few days

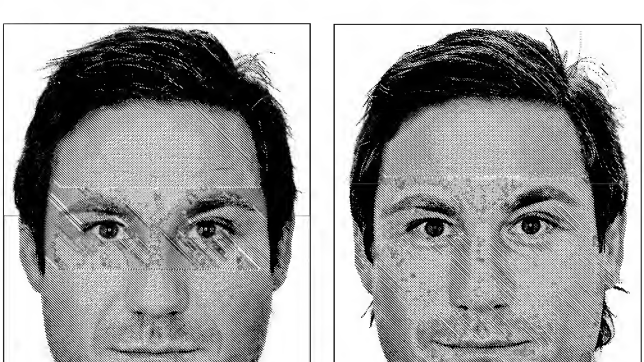

Figure 4. A, *Pretreatment view of a 35-year-old man who requested treatment of a forehead scar, nasolabial folds, and glabella fold.* **B,** *Posttreatment view 2 weeks after injection of Restylane for the forehead (3 mL) and Restylane Perlane for the nasolabial and glabellar folds (1 mL).*

after injection into the skin. Delayed, localized inflammatory reactions (1 in every 10,000 treatments) have been reported to occur with the Restylane products. These have consisted of swelling and induration at the implant site, sometimes accompanied by edema in the surrounding tissue. Erythema, tenderness and, in rare cases, acne form papules may occur. In pronounced cases, a short course of oral corticosteroids may prove effective.

Evidence From Clinical Trials

Extensive clinical experience gained from intradermal application of NASHA in over 3 million instant aesthetic treatments since its initial launch in 1996 confirms its effectiveness, safety, and extremely low risk of inflammatory reactions. Clinical studies indicate that NASHA gels are effective in augmenting the lips[12] and correcting marionette lines, facial wrinkles, and nasolabial folds.[12–17] Moreover, they offer a more durable aesthetic result than either bovine collagen[15,18] or avian hyaluronic acid.[19] Representative photographs of the aesthetic results obtained following treatment with intradermal NASHA preparations are shown in Figures 4 to 6.

A retrospective worldwide review of the tolerability of NASHA in facial soft-tissue augmentation showed that an adverse event was reported in 1 of every 650 patients (0.15%) treated with the product in 1999.[20] Treatment-related adverse events were transient and included redness, swelling, localized granulomatous reactions, and bacterial infection. Adverse event rates decreased to 1 in every 1800 patients (0.06%) in 2000 with the introduction of a more purified hyaluronic acid raw material. Inflammatory reaction was the most common adverse event, affecting 1 in every 5,000 patients.[20]

Restylane SubQ—a New NASHA Preparation Product

Restylane SubQ consists of the same NASHA gel used in other Restylane products, but it has a larger

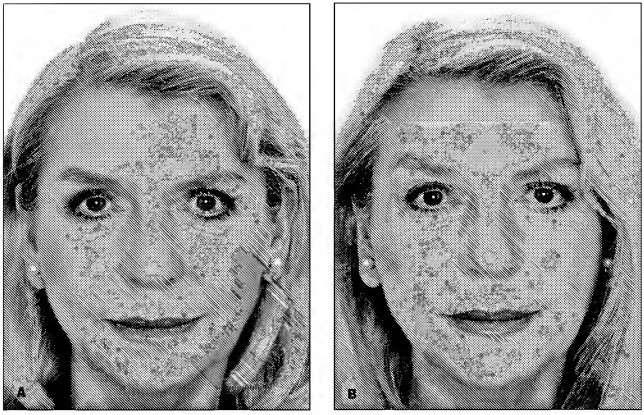

Figure 5. A, *Pretreatment view of a 67-year-old woman before correction of nasolabial folds, the glabella area, jawline, lipline, and corners of the mouth.* **B,** *Posttreatment view 2 weeks after injection of Restylane Perlane (1 mL) and Restylane (4 mL). Restylane was used for the nasolabial and glabellar folds and the lipline. Both Restylane and Restylane Perlane were used for the mouth corners.*

gel-particle size (approximately 1,000 particles/mL). It is intended for deep subcutaneous and/or supraperiostal injection to allow more extensive facial volume augmentation or sculpturing. The subcutis consists mainly of adipose tissue and is looser and less vascularized than the dermis, making it a more suitable matrix for implantation of Restylane SubQ. Possible indications for Restylane SubQ include augmentation of normal facial features (eg, malar and chin enhancement), facial reconstruction (eg, treatment of posttraumatic facial asymmetry), and correction of facial concave deformities. Another promising potential indication for Restylane SubQ is the treatment of HIV-associated facial lipoatrophy.

Treatment results are immediate and are estimated to last for at least 9 to 12 months after the initial treatment. Restylane SubQ is currently approved in Europe and can be used as an alternative or a complement to traditional face lifts. Preliminary (3-month) findings of a 12-month Canadian study of Restylane SubQ in cheek and chin augmentation indicated good efficacy, with the vast majority of patients (84%) and investigators (95%) reporting moderate or good cosmetic improvement at 3 months after the initial treatment.[21] The longest follow-up in the senior author's (A.V.) experience is 12 months, with full correction being retained at this time.

Conclusion

The use of injectable materials for soft tissue augmentation is becoming increasingly popular. Restylane is a NASHA gel that produces predictable and long-lasting instant aesthetic results. The newest product in the Restylane range, Restylane SubQ, is a large-volume, soft tissue filler suitable for facial augmentation and reconstruction. Ideal candidates for Restylane SubQ treatment include those requiring augmentation of normal cheeks and chin, reconstructive treatment, and correction of concave deformities. With the limited number of products currently available for this indication, Restylane SubQ offers a new treatment approach that is both safe and effective. ■

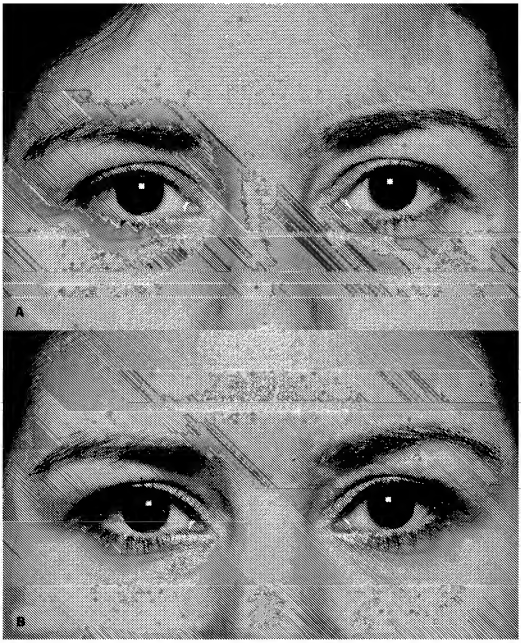

Figure 6. A, *Pretreatment view of a 39-year-old woman with deep tear troughs.* **B,** *Posttreatment view 2 months after administration of Restylane Perlane (0.3 mL on each side) deep on the orbital rim through 2 or 3 injection sites.*

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Restylane SubQ is not approved for any use by the US Food and Drug Administration.

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MATERIEL ET METHODES/EQUIPMENTS AND METHODS

Produit:

	Fournisseur / Numéro de lot
Bleu de toluidine	Fluka / 89640

Equipement:

	Modèle
Microscope binoculaire	Leica MS5

RESULTATS – DISCUSSION/RESULTS – DISCUSSION

- **Préparation d'une solution de bleu de toluidine**

[bleu de toluidine]= 6.9×10^{-4} g/ml (bleu de toluidine dans eau ppi) ≈ 0.1%

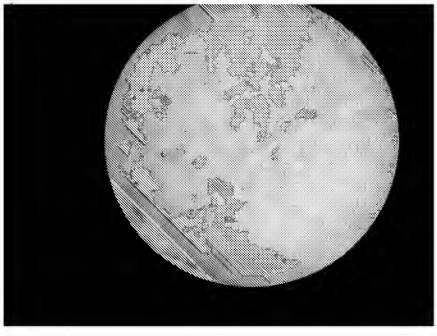
- **Coloration du gel avec le bleu de toluidine et observation au microscope**

La méthode qui a été utilisée dans cette étude est la suivante :

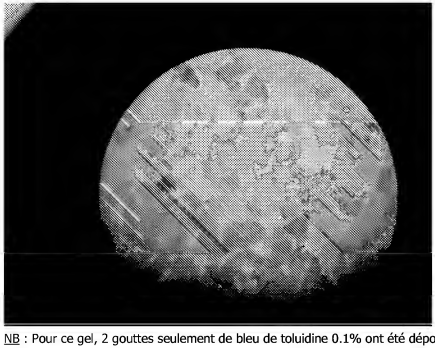
- 0.1g de gel est déposé sur une lame de verre.
- 5 gouttes de solution de bleu de toluidine à 0.1% sont ensuite déposées sur le gel.
- Après répartition de la solution colorante sur le gel et absorption de celle ci (dizaine de secondes), une lame de verre est déposée sur le gel.
- Le gel coloré est ensuite observé au microscope sous un grossissement X40.
- Une photo est prise à partir de la binoculaire.

- **Aspect des différents gels colorés observés au microscope (grossissement X40)**

✓ Restylane

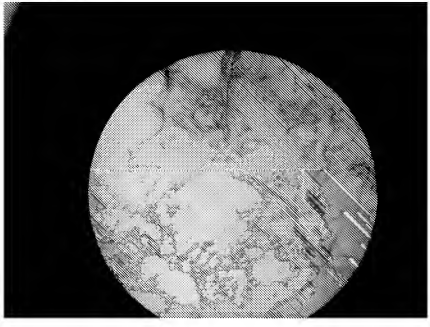


✓ Hylaform

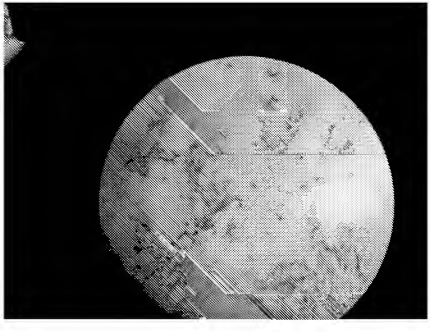


NB : Pour ce gel, 2 gouttes seulement de bleu de toluidine 0.1% ont été déposées sur le gel.

✓ Esthélis Basic



✓ Fortélis



CONCLUSION

➔ Les gels **Restylane et Hylaform** ont une structure différente des gels **Esthélis et Fortélis** (structure particulaire dans le cas de Restylane ou Hylaform).

Choosing Injectable Implants According to Treatment Area: The European Experience

Catherine Bergeret-Galley, M.D.[1]

ABSTRACT

There are now many injectable implants for face remodeling since the first product appeared in Europe in 1984. The treatment regions most in demand are the cheeks, jaws, lips, and the oval of the face. The aging process is due to fat resorption over the upper two thirds of the face, in addition to the loss of elasticity. Weakness in the skin and subcutaneous fascia becomes more apparent over the lower third of the face. The fat loss together with the slack skin gives the impression of gauntness and loss of volume under the eyes (i.e., the zygomatic and palpebral areas). Treating the zygomatic bone area and subcutaneous tissue by injecting filler products will increase volume around the zygomatic malar bone and subcutaneous area. To choose an implant, we must take into account the patient's wishes, hopes (whether temporary or long-lasting effects are required), age, skin type (dry, moist, greasy, thick, or thin), and the patient's medical history to prevent obvious contraindications in the choice of implant due to type of product, especially in the case of allergies, inflamed areas, or any suspicion of autoimmune disease or recent infection.

KEYWORDS: Collagen, hyaluronic acid, polylactic acids, calcium hydroxyapatite, polyacrylamides

The number of injectable products that can be used as fillers for treatment of wrinkles or as volume expanders on the face has grown dramatically since the first injectable collagens were put on the market in 1984 for treatment of wrinkles. This abundance means improved treatment for the patient, as well as proposing the most adapted treatment. The many products now made by the laboratories have also made prices competitive.

Remodeling the face using injectable implants has, for more than 5 years, been the number one rejuvenation treatment in the world, superseding peelings and surgical lifting procedures.

This situation creates a need for increased awareness by the practitioner and a good knowledge of the implants.

Most of the main injectable implants are all members of the large family of polysaccharides, which are sugars and have well-known benefits and complications. New products continue to arrive on the market with often incomplete chemical formulas, molecules that can more or less be identified, and, what is even more worrying, a total lack of clinical history with respect to tolerance, harmfulness, and absence or presence of long-term complication.

Its important to recognize that we cannot consider an injectable product safe from possible complications until it has performed through clinical studies over at least 5 years, which is practically never accomplished.[1]

Complications from the use of nonresorbable injections may therefore only appear years after the injections or as late as 15 to 20 years after

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Figure 1 Nasolabial folds. Juvéderm Ultra or Surgiderm 24 deep, superficial plane Juvéderm or Surgiderm 18, or Perlane and Restylane (Teosyal, Anthelis, Isogel, etc.), or Zyplast and Zyderm I or Zyderm II or Evolence.

injection, especially those containing silicone (e.g., siliconoma).

When remodeling the face, filling the troughs, and treating deep nasolabial ridges, we use volume expanders. When deciding on a temporary treatment for a young or undecided patient, we prefer using resorbable implants: high-density hyaluronic acid over the periosteal bone, together with lower-density hyaluronic acid (subdermally). Possible associations are Comeal Voluma + Surgiderm 30 or Surgiderm 24 (or Juvéderm 30 or Juvéderm 24) or Restylane SubQ+ Perlane or Restylane. The results are excellent for more than a year (Figs. 1–3). If, however, we need a more durable result under healthy thick skin, we could use Radiesse (particles of calcium hydroxyapatite in a methylcellulose suspension) subcutaneous injection (Fig. 4) or Derma-Deep (acrylic particles in a hyaluronic acid gel) over the malar bone and Juvéderm or Surgiderm 30 or Surgiderm 24 subcutaneously. Arteoll (polymethylmethacrylate particles in bovine collagen) can also be used for deep injections. We never use collagen as a volume expander; we will usually use reticulated hyaluronic acid. We also use a combination of lactic acid and glucose; New-Fill reticulated or Sculptra give good results in these cases. A new glucose-based injection, Easy Agarose, seems to be promising. Russian and Ukrainian scientific studies on the complications in using polyacrylamide-based injections on the face and body (breasts, hips, and penis) have shown them to be catastrophic and that all doctors should avoid these types of injectable implants (patient 3). Resorbable implants, especially hyaluronic acid and certain collagens, are very well known when treating moderate, superficial wrinkles. We always use the same retrograde injection technique, directing the needle from the deepest point toward the surface, or on the same plane, a method that will prevent contamination of the superficial dermis by the implant, particularly when using nonresorbable implants. Multipuncture techniques are often useful but must be reserved for resorbable products, having proved their harmlessness, essentially hyaluronic acid. These injections must be performed with experience and care.

THE PRODUCTS

We prefer resorbable products over the various injectable volume-filler implant, not only because they are well tolerated, but also because their quality is constantly being improved, in certain cases giving positive effects for as long as between 12 and 15 months, more than

Figure 2 Reshaping the face. Juvéderm 30 and Juvéderm 24 HV for the lips, the cheeks, and the jowl line. Voluma on the malar bones (always less than too much) or Restylane and Perlane + Restylane SubQ. Alternative New-Fill or Sculptra subcutaneously but not for the lips.

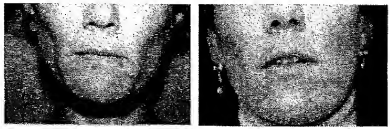

Figure 3 Cheek filling with Juvéderm and Voluma. Left: Before treatment. Right: 15 months after injection.

enough for a filler implant, especially when it has practically no complications.

In this study, I shall detail the different families of implants frequently used, for which we have sufficiently serious clinical and scientific history, with respect to their localization. Resorbable injectable implants belong to four large biochemical families: collagens, hyaluronic acids, sugar and lactic acid associations (New-Fill, Sculptra), and mixture of methylcellulose and calcium hydroxyapatite.

The Collagens

The first on the market were Zyderm and Zyplast (Allergan, Irvine, CA). They are still considered to be good implants for wrinkle treatment, but not as volume expanders. Zyderm and Zyplast are obtained from bovine collagen. This bovine collagen resource has been tested many times and has proved to be free of prions causing subacute bovine spongiform encephalopathy. Moreover, this collagen (class 4 tissue) is extracted from the dermis of animals that have never been infected with prion. Because of the strong species specificity of collagen, an allergy test is recommended.[2]

Even if two tests are performed before the first injection, each should be 4 to 5 weeks apart. There is still a 1.5% risk of allergic reaction after treatment with bovine collagen. Allergic reactions are essentially type 1, local or diffused (redness and edema), and will very rarely occur as type 4, retarded hypersensitivity with granulomatous inflammation.

In spite of this, Zyderm and Zyplast are always good collagen fillers for wrinkles, with an appreciable positive effect around the lips.[3]

Evolence is extracted from porcine collagen. Its interest resides in its negligible percentage of allergic reaction occurring after use. This is due to the modification in its chemical structure. Nevertheless, it is still possible to have allergic reaction.

The laboratory does not recommend any injectable test be performed. This implant is an interesting polyvalent filler, for use with small to more noticeable wrinkles, but it must be remembered that it is not considered a volume expander. It can be used in the case of mid to superficial wrinkles (not too superficial) but gives less interesting improvement than does thick hyaluronic acid in deep folds and wrinkles. The stability results of this filler are considered to be longer than those observed with Zyderm also. One should avoid injecting it in the epidermis and under thin skin; the slightest irregularity during implantation leads to a whitish chain of micronodules, which are not only totally unaesthetic but could last for many months, even years. The cystic nodules, proved to be formed by the neocollagen, are

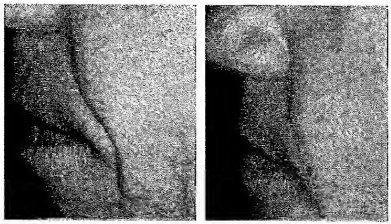

Figure 4 Nasolabial folds. Radiesse in the deep plane + Zyderm I or Juvéderm 18 (second session).

unfortunately to be found in the nasolabial folds but also jugulopalpebral fissures.[4] The lesions may resemble acne in the nasolabial fold, but this complication is usually common to all implants and could be due to the fact that this area is rich in pilosebaceous glands. Evolence should not, therefore, be used in the epidermis or in thin skin. The laboratory is enlarging its range with Evolence Breeze for rejuvenation of the lips (patient 4). As in all collagens, its injection is slightly painful in this region. It is therefore recommended that an injection of local anesthetic be proposed to the patient. The results are very limber, aesthetic, and lend themselves to a natural, soft, and homogenous appearance.

CosmoDerm and CosmoPlast are collagens extracted from the human dermis (prepuce skin).

These are good products, but of no particular interest in comparison with Zyplast. The collagen clearly guards an important immunologic specificity for the human being. The occurrence of an allergy in this type of collagen remains possible, but its duration is not considered to be longer than that occurring after the use of Zyderm or Zyplast.

The autologous collagen Autologen[5] was first marketed in the United States, followed by Isolagen. It is formed from a collagen taken from the patient himself (Autologen) or taken from collagen-producing fibroblast cultures, both taken from a skin biopsy. The production of 1 mL of Autologen requires a fairly large skin surface. Isolagen® is the most successful autologous collagen. The fibroblast culture is obtained after excision of the skin from the retro-auricular area. The sample must be handed to the laboratory in an isothermal container on the second day and cultured for 6 weeks. Five milliliters of Isolagen can thereby be obtained. A 1 mL syringe of autologous collagen can be reinjected during 2 to 3 sessions at 1-month intervals. They are conserved by the laboratory and then transferred to the doctor handling the patient. Autologous collagens are the products of an interesting technology, but which is costly and not proven to be beneficial when compared with reference collagen (Zyderm, Zyplast).

The Hyaluronic Acids

The best hyaluronic acids for use as fillers and volume expanders are reticulated hyaluronic acids. Hyaluronic acids are polysaccharides; the chemical reticulation allows the polysaccharide chains to bond together. The most commonly used reticulating agent is butanediol diglycidyl ether (BDDE). Other reticulating agents are being progressively abandoned because of complications, as with vinyl sulfur and formaldehyde. The reticulation of hyaluronic acids means they are resistant to degradation by heat or enzymatic action. The enzyme responsible for its degradation is hyaluronidase, but other enzymes may also interfere, not forgetting hydroxyl radicals produced by inflammation, during which their action is rapid. We can divide the hyaluronic implants into two major groups, depending on their three-dimensional nature of reticulation: the biphasic or monophasic implants.

THE BIPHASIC IMPLANTS: RESTYLANE, PERLANE, RESTYLANE SUBQ, AND HYLAFORM

Restylane (Q_Med) was the first hyaluronic acid to be marketed in 1996, as a wrinkle filler. It has continuously been improved since it was first manufactured and marketed. The hyaluronic acids are produced by bacterial cultures (*Streptococcus*). The bacterial stem was modified between 1999 and 2000, as well as the reticulation agent, which is now BDDE. The concept of biphasic implantation is related to the light reticulated macromolecular aggregates in a fluid suspension. The fluid is rapidly absorbed and provides good distribution of the macromolecules days after the implantation.[7]

As for Perlane and Restylane SubQ, the particles are bigger, with smaller particles floating in the fluid suspension. Nevertheless, it is always the same concentration of sodium hyaluronate (20 mg/mL), and it is only the size and number of the particles that change according to the implant. The U.S. Food and Drug Administration (FDA) authorized Restylane for cosmetic use[1,7–10] in the United States in 2001. Restylane SubQ has bigger particles, 1000 particles/mL gel, whereas Perlane has an average of 10,000 particles/mL. Restylane SubQ is considered one of the high-volume expansion hyaluronic acids and is very difficult to inject (Fig. 5). A large-bore needle has to be used, 16 to 19 gauge, or else with small catheters. Local anesthesia is highly recommended, and disinfection of the site should be done very carefully. Hylaform, which is produced by Genzyme, later acquired by Allergan, contains hyaluronic acid extracted from rooster combs. Some allergic incidents have left the product unpopular.

THE MONOPHASIC IMPLANTS

Voluma, Surgiderm, Juvéderm, Hydrafill, Teosyal, Anthelis, Puragen, Isogel, and so forth, are considered as a continuous polysaccharide chain related in a linear structure by reticular particles. These chains can be more or less thick with respect to the desired results, both in terms of their viscosity, elasticity, and according to the intensity of the implant and the amount of reticulation. The injection is theoretically more homogenous and easier to do.

The experience of the surgeon or doctor in guiding the hand and choice of the needle is of the utmost importance. The reticule is BDDE. The monophasic implants are numerous, for repetition, Juvéderm, Hydrafill, Surgiderm, and Voluma, which are all produced by the same laboratory, Corneal (France), acquired by Allergan (USA). The products are derived from the

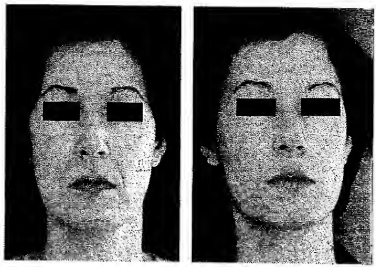

Figure 5 Botulinum toxin forehead, glabella, and periorbital area. Restylane SubQ on the malar bones. Juvéderm 30 on jowl line.

same concept. Surgiderm was born from a long evaluation of the biochemical concept of Juvéderm,[4] in the knowledge that the implant is very liquid, with an optimal degree of linear crosslinking allowing homogenous implantation and durability. Voluma can be compared with Restylane SubQ, as it is a very voluminous implant. Its action is derived from a thick hyaluronic acid reserved for deep planes (Fig. 6).

Between each chain there will always be reticules of BDDE nearby, together with smaller chains of polysaccharides. The reticular concentration is increased, but so is its effectiveness. The product has very good volume. A 16-, 19-, or 21-gauge needle should be used, or a small cannula after microincision of the skin using local anesthesia, or locoregional as with other thick injectable implants such as Restylane SubQ. The injection can only be performed on the periosteum or subcutaneously, but never within the dermis or thin skin. When using hyaluronic acid, effects such as localized edema may persist for more than 2 years. All hyaluronic acids absorb water and can multiply their volume by 5 at the very least; this effect is most noticeable when using thick hyaluronic acid. In conclusion, hyaluronic acids are resorbable injectable implants for both wrinkles and volume. They are all good quality as a rule, however, some are better than others; the complications related to this type of implant are mainly due to the permanence of protein residues from the bacterial strain and residual concentration while reticulating (toxic). We are very careful when mixing hyaluronic acid with macromolecules of the dextran type, which can block the arterial and venous capillaries, causing very significant inflammatory reactions and possible cutaneous necrosis of vascular origin. Several incidents have been reported. Products such as Matridex Beauty Sphere are to be prescribed.[11,12]

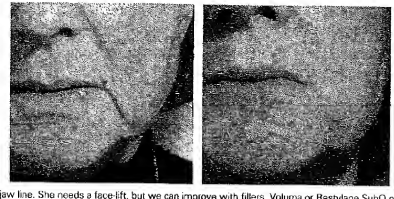

Figure 6 The jaw line. She needs a face-lift, but we can improve with fillers. Voluma or Restylane SubQ on the cheekbone, Juvéderm or Perlane in the cheeks, marionette lines, and the chin.

Polylactic Acids

Sculptra and New-Fill are two applications for the same implant. Sculptra is used for aesthetic purposes, whereas New-Fill, registered and reimbursed in France, is used for facial Lipo-atrophy in HIV-positive patients. Biopharmex Biotech, acquired by Sanofi Aventis, produces the product. These are polylactic acid molecules associated with sugar, carmellose, and mannitol in microspheres. It is a sterilized, freeze-dried powder that rehydrates using sterile water and a little Xylocaine (lidocaine). The injection is painful given the presence of lactic acid. Local anesthesia is recommended. It is best to mix the preparation 24 hours before the injection. The follow-up is rigorous and requires that the patient keep their appointments. It is primarily a volumizing product, so it must not be injected for wrinkle treatment or lip augmentation because its accumulation, particularly under thin skin, will lead to inflammatory granulomas, which can be unfortunately spectacular. The product is likewise capable of migrating to the nasolabial folds as well as the oval of the face.

As a volumizing agent, New-Fill injections will require three to four sessions with 1 month in between to get an optimal result. These injections should be repeated (5 times a year) to obtain the best results. The product is expensive, but the duration of the product is sufficient for HIV-positive patients who are socially handicapped by their facial lipodystrophy.

Other Fillers

Bioinblue is one of these new confidential products. It is manufactured by Polymekon, an Italian laboratory. It is a polyreticulated alcohol, semiresorbable implant, and takes the form of a homogeneous viscoelastic product, marketed as a lip and nasolabial fold filler. It is a biphasic water saturated implant producing a purely mechanical filling. The pain inflicted by the injections together with the significant inflammation, have lead to this product being dropped.

Radiesse is a semiresorbable implant containing calcium hydroxyapatite. It is manufactured by BioForm. Calcium hydroxyapatite has long been used for osteogenesis in semisolid protheses. When used for aesthetic purposes or in urology (for the bladder sphincter), where volume, fibrosis, or neocollagenesis is important, the concept is different.[13,14] The particles of calcium hydroxyapatite (45%) are suspended in a carboxymethylcellulose gel (65%). The implant is completely synthetic and biodegradable, but some macrospheres will not resorb. The product is whitish in color, thick, and difficult to inject, requiring 26- or 27-gauge needles. The irritation caused in the tissue can on the one hand increase collagen, but can also lead to the formation of granuloma. Taking its biochemical nature into account, this interesting implant has restricted aesthetic indication properties. Filling the nasolabial fold, especially when the skin is thick and the fold is deep, is an excellent indication. The filler can perform for more than 15 months. This product should be avoided in other areas, such as the lips, the area surrounding the mouth, thin skin, estrogen deficiency, and skin with acne. It is too early yet to speak about perfect harmlessness.

Implants containing nonresorbable fillers must be avoided on the face. We know that silicone liquids and paraffin are forbidden both in Europe and in the United States except for particularly well-documented studies concerning HIV-positive patients (two studies currently in the United States for injectable silicones).

Acrylate gels, such as Artecoll, ArteFill, DermaLive, DermaDeep, and Novasoft, must be used with caution.

I wish to spend a little time with respect to polyacrylamides, because although currently in fashion in Europe and the Middle East, they have been the cause of human disasters in the Ukraine, Russia, and China.

We know that although a product cannot be marketed in one country, it can reappear in another country under another name, marketed by another distributor and possibly produced by another laboratory, with the same chemical structure and the same scientific adviser. Thus, Royamid was forbidden in the Ukraine, but other polyacrylamides appeared on the international markets: Aquamid (Holland), Safe-fill (China, under UK license), Amazing Gel (China), Evolution, and Outline (France), Polymekon, an Italian laboratory, markets Bio-Alcamid, a polyalkylimide with a similar chemical structure to polyacrylamides.

Inoffensive nonresorbable implants remain to be found, so one must avoid their use for rejuvenation and facial embellishment.

CHOICE OF IMPLANT ACCORDING TO ITS INDICATION

Facial skin is unequal in nature, i.e., the cheeks, chin, and cheekbones are very different from the area surrounding the lips and periorbital areas, which are composed of thin skin with very fragile lymphatic capillaries.

The questionnaire and the medical history of the patient are essential, and photos should be taken prior to the first injections, and, if possible, 1 to 2 months after each new series of injections. One should make an appointment to see the patient 4 to 6 weeks after an injection, and then 3 months later to see the result. This will also give the practitioner the opportunity to check on tolerance of the product and to add a small amount when required. One should always inform the patient of the nature of the product and the expected duration, this should be done prior to the patient signing the information application, the consent form, and the estimate with all of the information at hand.

The medical history of each patient allows us to be informed of any prior medical incidents or to suspect that they have a potential problem thus avoiding contraindication. The notion of hyperactive autoimmune system or inflammatory diseases in either the patient or his or her immediate family are also important. Nonabsorbable as well as some absorbable implants are contraindicated. Even a reticulated hyaluronic acid of moderate density may trigger immediate inflammatory reactions (edema, redness), or later lead to nodules and inflammatory granuloma over an immune-deficient area.

Normally, injecting these types of patient should be avoided, but if it should prove necessary, it is best to use hyaluronic acid, which can be controlled.

Similarly, any infectious disease, either diffuse or local, is considered to be a veritable temporary contraindication. Sinusitis, dental abscess, herpes or other cutaneous eruptions are known to reactivate nodules and granulomas and can also create cystic lesions containing sterile pus as is the case of facial subcutaneous infection with Bio-Alcamid.

The nasolabial folds are a relatively simple indication, but all depends on the nature of the skin (thin, thick, dry, greasy, healthy, or pathologic).[15,16]

When performing a deep injection, use a thick reticulated hyaluronic acid, together with a reticulated or nonreticulated hyaluronic acid on the surface, from the same manufacturer if possible.

Possible associations are Perlane + Restylane[17] in the middle plane and Restylane Touch on the surface, or Restylane Vital to the subcutaneous tissue.

Juvéderm 30 or Surgiderm 30, Juvéderm 24 injected in the middle dermis if needed.

Juvéderm 24 HV or normal or Surgiderm 18 injected superficially in the dermis. The same goes for Teosyal, Isogel, or Anthelis, where the denser product should be injected into the deep dermis. Zyplast collagen is given subcutaneously and Zyderm I or Zyderm II more superficially. Evolence should be used for the deep or middle dermis.

Other associations are also possible whenever the patient has already proved good tolerance to the implant, knowing that allergic reactions arise most commonly when an alternative implant with a different chemical composition is injected on the same site or in a different cutaneous plane.[18]

Radiesse is best adapted by itself to the deep folds and can eventually be complemented with a fine hyaluronic acid.

Certain implants should not be used for the lips: Biocalmid, Radiesse, Beautysphere, and New-Fill. Others must be avoided even when patients insist on the nonabsorbable implant. The most efficient implants are the hyaluronic acids (except for the volume expanders), and collagens such as Zyplast, Zyderm, Evolence, or Evolence Breeze, which are designed for the lips.

Only fluid nonreticulated hyaluronic acids should be used for the forehead, particularly as mesotherapy.

The cheeks, the cheek bones, the brow, and the oval of the face are easy areas for treatment with respect to volume reconstitution, as long as one respects the following: thick or nonabsorbable implants injected deeply, and the more fluid implants injected into deep dermis or subcutaneously Under-correction is better than secondary overcorrecting due to implant excess or the positioning of the latter (hydration and enzymatic reaction will cause secondary edema of the viscous hyaluronic acid; patients 6 and 7).

For the over-periosteal area we choose Voluma + Juvéderm or Surgiderm 30 or Surgiderm 24 for subcutaneous, or Restylane SubQ or Perlane for the subcutaneous plane and Restylane for the deep plane.

Acrylates as Artecoll or DermaDeep could be injected deeply in the cheeks and temporal area.[18,19]

Finally, the orbital area is extremely fragile and requires great experience and care. The collagens leave a white deposit and so should be avoided (patient 8).

The hyaluronic acids or the autologous fat tissue are the best adapted, as this is such a dangerous and difficult area to implant (cases of blindness have been reported).

Hyaluronic acid is used thick and deep on the periosteum, and fluid but reticulated superficially. Thus, we can treat the palpebral circle, sunken eyes, and eyelids (Fig. 7).

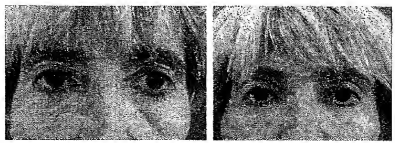

Figure 7 Periorbital rejuvenation. More difficult than expected especially after two eyelid surgeries; exclusively hyaluronic acid.

Wrinkles in the corner of the eyes can be treated by mesotherapy (intradermic or subcutaneous) or by injection of the superficial dermis with Juvéderm or Surgiderm 18 after treatment with botulinum toxin to get the best results.

CONCLUSION

Injectable implants contribute to facial beauty. Nevertheless, the following laws apply: caution and prudence at all times. Progressive training of injection technique is essential. Never inject an implant that you do not know. Always check the CE (Conformite Européenne [CE-marking indicates that the product complies with European safety standards]) norms and the technical leaflets provided with the implant packaging and check on traceability stickers.

Finally, carefully balance the patient's demands with respect to their medical history and the state of his or her skin.

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ISSUE 11 • NOVEMBER 2007

Clinical Study
with Monophasic Polydensified Hyaluronic Acid Filler Shows:

81 % Success Rate in the Treatment of Nasolabial Folds

A clinical study in 114 patients with nasolabial folds shows an impressive treatment effect of Belotero®, the first monophasic polydensified *hyaluronic* acid filler: 81 % of the patients were successfully treated for 24 weeks. The effect persisted 36 weeks in 66 % of the patients. According to the conclusion of experts at an international symposium during the 16th Congress of the European Academy of Dermatology and Venereology (EADV) in Vienna (Austria) this prolonged effect is probably due to the speciality of monophasic polydensified fillers.

The prospective multi-centre clinical trial was carried out in four centres in Germany. Participants were volunteers with symmetric bilateral nasolabial folds seeking for correction. The treatment period was 24 weeks. Thereafter, patients could participate in an optional follow-up period of 12 weeks. All participating physicians had several options for an injection technique (linear, stratum, fan or a combination). According to the study protocol the implant was injected bilaterally in the nasolabial folds, touch-ups were not permitted.

Treatment results were evaluated immediately before (baseline) and after the injections as well as two, four, 12 and 24 weeks after the implantation. Treatments were performed by two dermatologists (Prof. V. Steinkraus, Hamburg; Dr. K. Dirting, Hanau) and two plastic surgeons (Dr. M. Wolters/Dr. H. Lampe, Frankfurt; Dr. J. Reinmueller, Wiesbaden), all being experienced in aesthetic medicine. In addition an independent dermatologist rated the effect of the treatment using standardised photo documentation.

Severity of nasolabial folds was rated according to an international standardised score-system (Wrinkle Severity Rating Scale WSRS, Fig. 1). Treatment success was defined as at least one grade improvement in the WSRS-rating scale. The final evaluation was carried out at the end of the follow-up period after 36 weeks.

Primary endpoint was defined as efficacy of treatment after 24 weeks. In addition changes of WSRS-values to pre-treatment-values at different times after baseline were assessed. Only volunteers with WSRS-grade 3–4 (moderate to severe) nasolabial folds were included into the study.

Frequency and severity of adverse events were evaluated during and after the implantation. Implant area was examined during all visits.

Clinical efficacy, as well as tolerability was judged by physician and volunteers.

114 volunteers (11 men and 103 women) were treated, 109 completed the treatment period, 35 the optional follow-up. Age of subjects in the treatment group ranged between 30 and 60 years (average 50 years). Results of the trial were presented by the plastic surgeons Dr. Johannes Reinmüller, Wiesbaden (Germany) and Dr. Marianne Wolters, Frankfurt (Germany), who participated in the study.

98 % of Patients Rate Treatment Success as Good or Very Good

"Even immediately after the implantation we found a distinct and significant improvement of the nasolabial folds in 93% of the patients", explains Dr. Wolters.

After week 24 an improvement of at least one degree in the WSRS-rating scale could be seen in 81% of the patients. Success of treatment was age-related, but even in patients over 50 years of age a 1 degree WSRS-improvement was still achieved in 79% of the cases.

98% of all patients and 90% of the examiners rated treatment success as good or very good. Fig. 2 illustrates treatment success up to week 36.

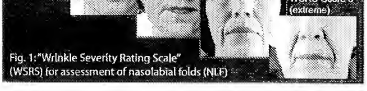

Fig. 1: "Wrinkle Severity Rating Scale" (WSRS) for assessment of nasolabial folds (NLF)

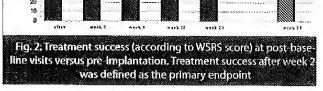

Fig. 2: Treatment success (according to WSRS score) at post-baseline visits versus pre-implantation. Treatment success after week 2 was defined as the primary endpoint

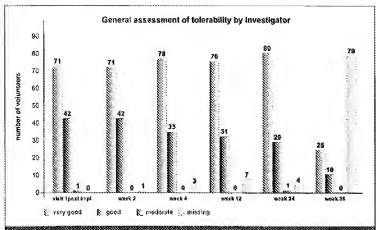

Fig. 3: General assessment of tolerability by investigator

"We found the long-lasting effect amazing", said Dr. Reinmüller. "The ideal dermal filler should be non-permanent, but with a durable effect. In our study even at the end of the follow-up period after 36 weeks, a treatment success was evident in 66% of all patients". In his opinion this could be explained by the special CPM® (Cohesive Polydensified Matrix) production technology making a big difference to conventional Hyaluronic Acid (HA) fillers. The structure of the stable matrix completely fills the intra-dermal space and hence leads to a lasting and natural cosmetic result with soft dermal transitions.

...With an Overall Good Tolerability Profile

Treatment was generally well tolerated. There were no serious side effects related to study treatment or adverse events that lead to study withdrawal. The most frequent side effects were local reactions at the injection site (haematoma, erythema or swelling in 22–25% of the patient population), as would be expected with every dermal filler application.

Overall after week 24 90% of the investigators rated the tolerability as good or very good. They assessed a good or very good tolerability in 109 out of 114 patients (Fig. 3).

Belotero®: A CPM®-technology based HA-Filler:

Easy Handling, Smooth Spreading in the Tissue

Hyaluronic acid dermal fillers represent the fastest growing non-invasive aesthetic procedure in the United States and many other countries, mainly due to their good benefit-risk ratio. Monophasic polydensified fillers combine the advantage of easy handling and smooth transitions between treated and untreated regions, thus creating a smooth natural look and feel.

Hyaluronic Acid (HA) fillers have become the gold standard for dermal enhancement and have been used in dermatology since 1990. The source of the first products was rooster's combs, but soon HA products were produced by means of the biotechnological method of bacterial fermentation. HA has a dry weight of only 3,5 mg/ml, whereas collagen comes to a dry weight of 65 mg/ml; highlighting the big difference in water binding capacity. Soon the cross-linking technique was introduced to stabilize HA and get a longer half-life and thus a more durable treatment effect.

A significant progress in filler development was the introduction of the Cohesive Polydensified Matrix (CPM®)-Technology. "By means of this new technique of cross-linking we obtain a material with very low viscosity and high elasticity" explains Dr. Reinmüller. The result is a hydro-gel with a matrix having dense and less dense zones, which is still cohesive.

This is a big difference to the conventional HA-filler, consisting of two phases: insoluble cross-linked HA-particles and liquid native hyaluronic acid. If HA is completely cross-linked, it turns into a solid block. Therefore it has to be crushed into particles. These particles are mixed with native fluid HA, to be able to inject it. One practical consequence of the different manufacturing process consists in the fact that fillers with CPM®-Technology optimally spread into surrounding tissue, as bigger gaps are filled with the denser parts. Even finest fissures can be entered by molecule parts with low viscosity. As the molecule stays coherent, the transitions between treated and untreated regions are smooth (Fig. 4). In contrast, the filling capacity of the conventional filler is limited by the

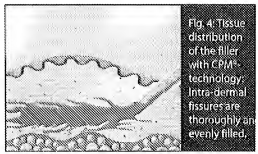

Fig. 4: Tissue distribution of the filler with CPM®-technology: Intra-dermal fissures are thoroughly and evenly filled.

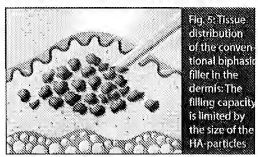

Fig. 5: Tissue distribution of the conventional biphasic filler in the dermis: The filling capacity is limited by the size of the HA-particles.

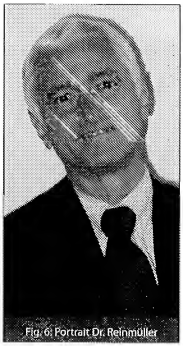

Fig. 6: Portrait Dr. Reinmüller

size of the particles: therefore finest gaps cannot be filled (Fig. 5). In addition particles always carry the risk of building bumps. Dr. Reinmüller cited here an example taken from road construction. Biphasic HA-implants fill wrinkles like potholes being corrected by pebbles, as opposed to pot holes being corrected by tarmac. The latter represents an example for the monophasic polydensified filler. Conventional filler products vary in particle size. But smaller particles that could fill narrow gaps have the disadvantage of being degraded more rapidly by offering degrading enzymes like hyaluronidase more overall surface.

Smooth Consistency Facilitates Implantation Process

Another practical advantage is the easy handling of the monophasic polydensified filler: The smooth consistency gel enables a low, even injection pressure for easy administration and comfort, thereby causing less implanting pain to the patient. "The handling of Belotero® is as easy as we know it from collagen – but without the known risks", concluded Dr. Reinmüller.

Corrections of Nasolabial Folds with a Monophasic Polydensified Filler:

Superior Efficacy and Tolerability

Interview with Dr. Johannes Reinmüller, MD, Plastic Surgeon in Wiesbaden, Principle Investigator of the Study

What are the most important results of this study?

In my opinion there are predominantly three points of interest: Most importantly we know that this monophasic polydensified filler is a safe product. As the correction of wrinkles by injection of HA-based fillers is an optional medical procedure and not a live-saving treatment, safety is really an important issue. In these types of treatments the first and foremost rule is: no harm.

A second really important result is that this treatment has a proven efficacy. In many other products we do not have any clinical study results. Here we know we have a reliable product.

Last but not least a comparison to a previous study[1] on two competing dermal fillers showed that the cohesive polydensified monophasic HA-based filler is superior to the biphasic product and to collagen preparations.

Do you have an explanation for the long lasting treatment effect?

We certainly are not dealing with isovolumetric degradation! At the moment we only have poor knowledge about the biodegradation of dermal fillers in vivo. Most of our data result from in-vitro-studies. Therefore I can only give you my personal explanation which is partly hypothetical and not established knowledge. By injecting any kind of filler material you always have to take into account that part of it is migrating, especially in products containing particles, solid or gel-like. Strictly speaking, this is a loss of material at the implantation site and not biodegradation in the sense of enzymatic breakdown or lysis. As a result of migration or dislocation the total amount of filler substance at the injection site is reduced during the entire observation time.

The remainder undergoes biodegradation, if possible. How this is accomplished on a molecular basis is not well understood in most biodegradable filler materials. In my personal opinion in the case of hyaluronic acids and its derivatives, the material is degraded by macrophages and cells of the immune system.

My explanation for the longevity of the cohesive polydensified monophasic product is: the material is anchored in the tissue. Since even finest fissures are filled with the cohesive material, it is indented in the tissue. Migration is less probable and we do expect more of the injected material to keep its position.

In what respect can the present study with the monophasic polydensified filler be compared with the study by Narins et al.? There are no head-to head comparisons between different hyaluronic acid fillers.

The present study was an open trial, whereas the study by Narins et al. was controlled and doubleblinded. But these studies had also very much in common: the patients had similar demographic and baseline characteristics. I think, the only meaningful difference between these studies is that in the older study two touch-up treatments were allowed.

If you take a close look at the results of this study, you notice that the monophasic polydensified filler is superior to the other products. With a single treatment we achieved a better effect compared to the competing products, where more than a third of the patients got touch-up-treatments.

1 Rhoda S. Narins, et al. A randomized double-blind multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of the nasolabial folds. Dermatol Surg 2003; 29:588-595

How was the tolerability in these studies?
You have to differentiate between side effects due to the product itself and side effects in connection with the implantation of the material, e.g. bleeding, swelling or erythema. But even if you take this into account, the monophasic polydensified filler was better tolerated. There were more side-effects immediately after implantation in the preceding study. Most patients in the study assessed the tolerability as good or very good.

Case Report:

Correction of Nasolabial Folds With a Monophasic Polydensified Filler

A 42 year old woman presented to the clinic with the desire for having her nasolabial folds corrected. The healthy patient had a history of allergy to nickel.

Before treatment the investigator rated her nasolabial-folds to be WSRS-grade 4 (Fig. 7a). A topical preparation of a local anaesthetic (Emla®) was applied to the injection site before implantation to minimize pain during the procedure. The investigator injected the material (Belotero®) via stratum technique.

Immediately after the procedure investigator and patient assessed that the folds had "very much improved". Fig. 7b shows a marked improvement of the nasolabial folds. The investigator rated the WSRS-score 2 after treatment.

The patient came to a control visit after 15 days. All further presentations on day 29, 82, 166 and 251 showed that the treatment effect was still evident, even 251 (Fig. 8) days after the initial treatment. During each visit the WSRS-value was rated 2 by the investigator.

During every visit investigator and patient shared the opinion that the folds had improved a lot.

The treatment was also judged by a reviewer based on photo-documentation. In his opinion, the WSRS-values at baseline were even 5. On the other visits he rated them to be 2, which comes to an improvement in the WSRS-scale of 3 points.

Noticeable was the long filling state of the nasolabial fold. The investigator judged the filling state to be 100% even on day 166 after implantation and 92% at the end of the follow-up treatment period.

Tolerability was fairly good. There were only mild side effects related to the injection like erythema, swelling and haematoma which resolved within a week.

The patient seeks no further treatment at the moment, because she is very content with the present situation.

This case report shows that in selected patients the treatment effect of a monophasic polydensified filler on the basis of hyaluronic acid can last up to nine months.

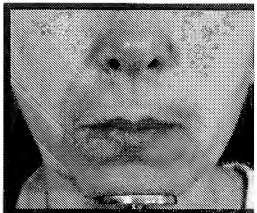

Fig. 8: Patient on day 251: The treatment effect is still evident. The patient see no need for a further treatment at the moment.

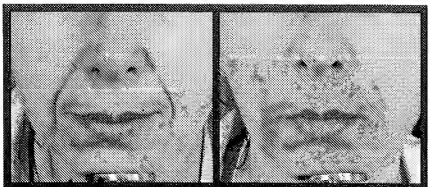

Fig. 7a: Patient before treatment: Although the volunteer is only 42 years of age, there are pronounced and deep nasolabial folds.

Fig. 7b: Patient immediately after treatment. Folds are far less evident.

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Esthélis®, hyaluronic acid of Swiss design. First complete study of the physico-chemical characteristics and clinical trials.

A. Bezzola · P. Micheels
Geneva, Switzerland

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Esthélis®, hyaluronic acid of Swiss design. First complete study of the physico-chemical characteristics and clinical trials.

A. Bezzola · P. Micheels*
Geneva, Switzerland

Since 1995, injectable hyaluronic acid has been presented as the product which should replace injectable bovine collagen.
Hyaluronic acid is present throughout nature and is a combination of disaccharide units of glucuronic acid and N-acetyl glucosamine (R.M.M. 400 Daltons) repeated infinitely (10.000 units and even more, R.M.M. > 4 million Daltons). It is polyionic and has an axial hydrophobic part and a central hydrophilic part.

There are 7 to 8 grams of hyaluronic acid in adults, 50 % of which (3.5-4.0 g) are found in the skin. It is distributed: ~0.5 mg/g in the dermis and ~0.1 mg/g in the epidermis. It is not specific to species or organs and is theoretically without risk of promoting allergy or causing a foreign body reaction.

Note that the length of the disaccharide unit is ~1 nm, i.e. up to 10 microns long (the size of a red blood cell) for 10,000 units.

As it is very sensitive to hyaluronidases (3 classes: a hyaluronidase and 2 exoglycocaidases), the half life of native hyaluronic acid is only ~3 minutes, through less than a day, to 2 to 3 weeks depending on the organ studied (blood, keratinocyte or chondrocyte).

In order to make it a wrinkle filling product which has some sustainability over time it needed to be cross-linked, whether it was extracted from coxcomb or from a culture of Streptococcus Equinus.

At present 2 molecules are used for this purpose, vinylsulfone for cross-linking through the hydroxyl groups for Hylaform® (basis of Hylan B), extracted from coxcomb and marketed by the Genzyme company (USA) (1, 2).
The cross-linking agent for the other hyaluronic acid extracted from a bacterial culture is BDDE (1,4-butanediol diglycidyl ether), which is the least toxic.

These chemical and stereometric manipulations of the native molecule are perhaps the origin of cases which we amongst others have reported in 2001, and which have increased in number since then from 8 to 16 patients (November, 2004) (3, 4, 5, 6, 12).

The 3rd molecule is used to cross-link Hylan A and is extracted from coxcomb: formaldehyde. There are 2 types of presentation of injectable hyaluronic acid on the market at present.

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Esthélis®, hyaluronic acid of Swiss design. First complete study of the physico-chemical characteristics and clinical trials.

The first comprises the Hylaform®-Gonzyme range (bird origin) and the Restylane®-Q-med range (bacterial origin) (4). These 2 presentations have the common feature of being biphasic injectable substances, with particles of hyaluronic acid cross-linked in a greater or lesser degree (<100 mm in the dry preparations but in this really the case in the syringe?) (4, 5, 7, 8) suspended in a more fluid or even non-cross-linked preparation.

The second is the monophasic gel preparation of hyaluronic acid contained in all of the other products which have been used (Juvéderm®, Hydra Fill® and finally, Esthélis®).

We note however that despite the purity of the product, we are aware to date of 2 patients (not injected by ourselves) who developed a severe inflammatory reaction after injection of Juvéderm® with a strongly positive intradermal test and anti-Juvéderm® antibodies (Prof Sainte Laudy's laboratory, Paris-France).

1. MATERIALS

1.1 Presentation

Macroscopically, Esthélis® is presented as a clear, colourless, transparent gel, sterilised by autoclave, in a glass syringe which is also sterile. In order to preserve all of its rheological properties (see below) and therefore to ensure a longer in vivo lifetime it is recommended that Esthélis® be injected through a

- 27 G needle for Esthélis® Basic and Men
- 30 G needle for Esthélis® Soft, (Curve 1).

Finally, the ergonomics of the syringe plunger is particularly well suited to the injections and the low pressure which needs to be exerted by the thumb for the hyaluronic acid to be correctly injected.

1.2 Composition

Esthélis® Basic and Men contain 22.5 mg/ml of hyaluronic acid and Esthélis® Soft contains 20 mg/ml extracted from a culture of equine Streptococcus, NaCl (0.9 %), water for injection, phosphate buffer to ensure good pH stability (mean: 7.0) and osmolarity (mean: 305 mOsm) - Sterilised by autoclave, pyrogen free.

Curve 1: Effect on viscosity and elasticity of passing Esthélis® Basic through a 27 G and 30 G needle at 1 Hz.
(Reproduced with the kind permission of Anton S.A.)

N.B.: At present Esthélis® Men has the same composition as Esthélis® Basic although its packaging is specifically different and is very masculine in design, as the market for male aesthetics is expanding greatly.

1.3 Chemical analysis

Data on 3 batches*	Esthélis® Basic	Esthélis® Soft
Hyaluronic acid (mg/ml)	22.5	20
NaCl (mg/ml)	9	9
Sterile water for injection	97.75 %	98 %
Phosphate buffer solution	q.s. 1 g	q.s. 1 g
pH (6.8-7.4)	7.0	7.0
Osmolarity (280-330 mosm)	305	298 (1 batches)

** Data published with the kind permission of Anton S.A*

1.4 Assays of "contaminants"

	- Protein residues (23-28-35 ug/ml) - Assay method	Endotoxin (0.07 à 0.14 EU/ml)
Esthélis® (3 batches)*	- mean: 28.66 - Lowry method	mean: 0.103

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1.5 Manufacturing technique

After linearising the spine of the native hyaluronic acid, cross-linking is started by adding BDDE. Dynamic cross-linking (patent registered) allows a product to be obtained which therefore macroscopically has a homogeneous appearance, and microscopically has a heterogeneous appearance. This patented technique allows what is called a *Cohesive Polydensified Matrix* to be obtained.

Placed in the presence of 1 ml of water for 2 minutes, the gel remains cohesive, which is not the case for biphasic products in which the "macroparticle" component appears immediately (7) (photo 1). The same applies after 24h in Tubes dye no. 548, the technique which we were using as early as 2001 (3).

2. PHYSICO-CHEMICAL STUDY

2.1 Visco-elastic properties

The visco-elastic properties of Esthélis® make it a substance which sculpts perfectly in the tissue, with very gentle massage to position it correctly.
It does not leave an "implanted cord" feeling and can even be referred to as having a lifting effect.

Esthélis®, hyaluronic acid of Swiss design. First complete study of the physico-chemical characteristics and clinical trials.

Photo 1a, 0.5ml Esthélis®
Photo 1b, 0.5ml Restylane®
Photo 1c, 0.5ml Hylaform® after 2 minutes in 1 ml of water

Clinically, patients have also commented on a hydrating effect in the treated area with, for example, abolition of crow's feet during treatment of the cheeks

2.2 Degradation

Theoretically, the parts of the Esthélis® matrix have uniform degradation kinetics. Substances of biphasic composition follow a biphasic degradation curve, a rapid phase for the fluid part carrying "pearls" of hyaluronic acid and a slower phase for the pearls (curve 2a).

2.3 Histology

We have been able to perform allergy screening intradermal tests in 3 of our patients who were allergic to Hylaform® and/or Restylane® (3).
There were no clinical reactions in the intradermal tests, except for 1 case of local erythema or even slight pruritis which lasted for a maximum of 24 to 48h in one of these patients. This patient agreed to undergo repeated biopsies over 1 month following a protocol from Dr D Sarazin at the Weintraub laboratory, Geneva, Switzerland and controlled by the Catholic University of Louvainen Woluwe (Brussels-Belgium).

Esthélis®, hyaluronic acid of Swiss design. First complete study of the physico-chemical characteristics and clinical trials.

"At 24 and 72 hours and again at 1 month, only exogenous material compatible with hyaluronic acid was found.
For the samples at 24 and 72 hours we found traces of a slight non-specific inflammatory reaction".

This diagnosis was confirmed by Prof. J.M. Lachapelle (Catholic University of Louvain-Belgium-Department of Dermatology-Allergology) who confirmed the complete absence of any foreign body granulomatous reaction on 5 different stains.

2.4 Modelling of resorption

We do not take account of the influence:

- of physiological effects which vary between patients (activity of hyaluronidases, oxidative effects etc.),
- lifestyle and external effects (U.V., cigarettes, mobility of the treated area, etc.).

The biphasic products
On the theoretical model, the more fluid "carrier" part is resorbed in 15 days to 1 month. This leaves the pearls of highly cross-linked hyaluronic acid which theoretically have an average resorption period of between 5 and 8 months following curve 2a below.

Esthélis®
Because of its monophasic nature with a cohesive polydensified matrix, Esthélis® has (still theoretically) non-abrupt, slower resorption than the biphasics for the first 4 to 5 months, followed by a second period of 3 to 4 months with degradation which may be slightly faster than the biphasics (curve 2a).

This indicates to us that if we compare the biphasic products with Esthélis® in theory, in order to obtain sufficient correction for at least 9 months, 2 to 3 injection sessions of the biphasics (9.9) are needed compared to 2 sessions for Esthélis®.

2.5 In theory

Considering the following (curve 2b):

D0
100 % correction, identical to both types of products.

D30
- The biphasic products: Because of the disappearance of the fluid phase only ~70 % of the substance remains requiring a second injection to keep correction at the 90 to 100 % level.
- Esthélis®: For the same period, the loss would only be 15 % instead of 30 % for the biphasics.

D60-75
- The biphasics: Without a booster injection on D30, only 50 % of the substance initially injected remains. 75 % of the substance remains with the booster injection on D30.
- Esthélis®: Following the resorption curve, 55-65 % of the substance remains, at which point a filling injection is required, particularly in areas subject to high mechanical forces (D60).

Theoretical resorption curve of Esthélis® over 7 months.
Theoretical resorption curve of the 1st accelerated component of a biphasic hyaluronic acid over 7 months

Curve 2a

Curve 2b: comparison of the gradual reduction between biphasic hyaluronic acid products and Esthélis®
(Reproduction permitted with the kind agreement of Anteis S.A.)

D90
- The biphasics: At the time of the 3rd injection the resorption curve shows that 75 % of the substance remains.
- Esthélis®: Without the further injection on D75, only 55 % of the substance initially injected remains. With this injection on D75, more than 95 % of correction remains.

D105
It is at this point when theoretically the resorption curves for Esthélis® and the biphasics cross if only one injection is performed, with slightly faster resorption of Esthélis® than of the biphasics.

D195
With the 3 injections of biphasics and 2 injections of Esthélis®: 60 % correction remains for each of the 2 types of products at 6 months. It will take a further 3 to 5 months of degradation of Esthélis® to return to the initial state.

We should note, however, that resorption depends amongst other things on the activity of each person's individual hyaluronidases and that these may be more or less active!

3. CLINICAL TRIAL

Our experience with Esthélis® Basic began in February 2004, and in September 2004 for Esthélis® Soft.

We would state that the protocol which we followed rigorously was extremely strict, and the doses which could be administered were very small with, for example, a maximum of a half syringe for a nasal furrow.
It is possible that our observations would have been different if we had injected more initially.

3.1 Injection techniques

As for all of the injectable hyaluronic acids we used point by point injection techniques which are better suited for Esthélis® Soft and the retro-tracing or even grognale technique for Esthélis® Basic.
As always, the injections were administered either into the superficial dermis, blanket method with the whitening technique or into the middle or deep dermis. Are these concepts still well founded since the work of doctors Flebrant and Colignon [10]?

Esthélis®, hyaluronic acid of Swiss design. First complete study of the physico-chemical characteristics and clinical trials.

3.2 Patients

We had the opportunity of treating 10 and 10 women followed by 4 and 1 (not reviewed after D30) men. No patients dropped out of the trial and patients were followed up very regularly from D0 to D180 (D3-4, D15 (+ 5D), D30 (+15), then + once per month) in the strict context of the trial, in a total of 25 patients and in 14 and 12 women plus 5 additional men in parallel with a follow up time from D0 to D150 (D3-4, then + every 30 to 60 days).

3.3 Areas treated

In the product registration study, only the following areas were treated, with maximum amounts of the product used set precisely, and only using Esthélis® Basic:

- Nasal furrows, treated with 0.3 to 0.5 ml per side (8 + 8 subjects).
- Glabellar region, treated with 0.1 to 0.3 ml (4 + 2 subjects).
- Lips treated, with 0.2 to 0.5 ml per lip (3 + 5 subjects).

We also treated skin cracks and even peri-oral lines as these 2 areas fall into the context of treatment of ageing lips. In curiosity, and in order to compare the problems seen with other injectable hyaluronic acids already present on the market which produce translucent cords (11, 12, 13, 14, 15) (photo 2) in areas with thin skin, we also treated cheek wrinkles in one patient.

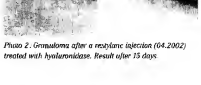

Photo 2: Granuloma after a restylane injection (04.2002) treated with hyaluronidase. Result after 15 days.

Esthélis®, hyaluronic acid of Swiss design. First complete study of the physico-chemical characteristics and clinical trials

4. TRIALS ON ESTHÉLIS® SOFT

It is desirable that a liquid filling product be used for all thin skins and thin wrinkles. The visco-elastic properties of Esthélis' Soft make it a product with similar result to the perfect result of collagen injections without the risk of white deposits appearing in the treated area as hyaluronic acid is colourless (photos 3, 4).

Since the 16th September, 2004 we treated the following areas in a total of 11 patients:

- Crow's feet (2 female patients)
- Peri-oral lines (6 female patients)
- Forehead (1 female patient)
- Fine nasal furrows (1 female and 1 male patient)
- Smoothing of the red part of the lip (1 female patient) (16)
- Bitterness folds (1 male patient)
- Wrinkles between breasts, and scars (1 female patient)

4.1 Side effects

Pain: For all the injectable hyaluronic acids for aesthetic use there is unfortunately no lidocain in the syringe which would make the injection almost painless.
In the most sensitive patients however application of an anaesthetic cream makes the procedure little or non painless and nerve trunk anaesthesia may be welcomed around the outline of the mouth.
Oedema: Slight oedema was seen particularly in the lip for 1 to 3 days disappearing without any pharmacological assistance.
Bruising/haematomas: Bruising or at worst haematoma may occur particularly in the lip region as may occur with any injection.
Intravascular injection: Intravascular injection is always conceivable, carrying a risk of necrosis.
Translucent deposits: With Esthélis' Basic injected into areas of fine skin we have seen, like the other injectable hyaluronic acids, fine translucent to blue coloured or even red coloured cords remaining for at least 6 months without hyaluronidase treatment. This applies to the other hyaluronic acids marketed for medical aesthetics.
Erythema: Post-injection erythema may develop. This may happen after any other aesthetic implant and may last for 48 to a maximum of 72 hours in our current experience.

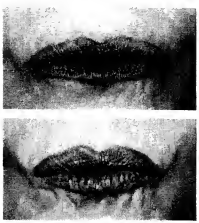

Photo 3a and 3b. Esthélis' Soft. Treatment of the perioral wrinkles on the upper lip

Photo 4 : Esthélis' Soft. Result after 1 month.

Trials on Esthelis' Basic (14 patients and 11 patients) Table produced in mid November 2004

Patient	Sex	Areas treated	Amount injected per session (ml)	Number of treatments	Persistence over time - follow up (months)
1	M	- Lips (larger desired)	1.0 - 1.0	2 (February - June)	4 - 9
2	F	- Upper lip (correction)	0.3	1 (May)	6 1/2 - 6 1/2
3	F	- Nasal furrows	1.0 - 0.4	2 (May - November)	6 - 6
4	F	- Glabellar area	0.3	1 (May)	4 - 6
5	F	- Lips + perioral lines - Bitterness folds - Nasal furrows	2.0	1 (April)	7 - 7
6	M	- Nasal furrows	1.0	1 (May)	6 - 6
7	F	- Bitterness folds	0.8 - 0.4	2 (April - August)	4 - 7
8	F	- Glabellar area - Bitterness folds - Nasal furrows	1.5	1 (May)	3 - 6
9	F	- Bitterness folds - Base of nasal furrows	0.8	1 (May)	6 - 6
10	F	- Bitterness folds - Base of nasal furrows - Top of V filter - Cheek wrinkles	1.0	1 (May)	6 - 6
11	F	- Glabellar area - Bitterness folds - Horizontal lines	1.0	1 (May)	6 - 6
12	M	- Nasal furrows	1.0	1 (May)	4 - 6
13	F	- Peri-oral lines - Cheek folds - Glabellar area	1.0	1 (May)	6 - 6
14	M	- Nasal furrows	1.0 - 1.0	2 (May - September)	4 - 6
1'	F	- Nasal furrows	1.0	1 (April)	5
2'	F	- Nasal furrows - Cracks	1.0	1 (April)	5 (NF) - 3 (crack)
3'	F	- Nasal furrows	1.0	1 (May)	6
4'	F	- Nasal furrows - Upper lip	1.0	1 (May)	5 (NF) - 6 (Lip)
5'	F	- Glabellar area - Nasal furrows	1.0	1 (May)	3 (GL) - 6 (NF)
6'	F	- Lips - Cracks	1.0	2 (May)	5
7'	M	- Glabellar area - Forehead wrinkles	1.0	1 (May)	Not reviewed
8'	F	- Nasal furrows	1.0	1 (May)	5
9'	F	- Nasal furrows - Cracks	1.0	1 (May)	4
10'	F	- Lips	1.0	2 (May)	4
11'	F	- Nasal furrows	1.0	1 (May)	5

10 women (mean age 57 1/3 years (1936-1967), 4 men (mean age 40 3/4 years (1958-1964)
10 women (mean age 43 years (1949-1966), 1 man (44 years)

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Infections: To date we have not seen any infection of the treated area although this is theoretically possible.
Necrosis: In absolute terms, intravascular injection which may cause necrosis is always a possibility.
Granulomas-allergy: We have not to date, i.e. with a follow up period of more than 9 months seen the least inflammatory granuloma or the least suspicion of clinical reaction similar to the allergies described for bovine collagen or the other hyaluronic acids which we have discussed above (3, 4, 5, 6, 12).

Note that we tested 3 patients allergic both to Hylaform® and Restylane® (3) with 2 intradermal tests 15 days apart, one of which even underwent a biopsy though had no side effects where the tests were performed. Two of these have been treated since with no immediate or medium term (3 months) problem.

Trials - Esthélis® Soft Table produced on 15 November 2004

	P-M	Crow's feet (ml/side)	Peri-oral lines (ml)	Forehead (ml)	Nasal wrinkle (ml/side)	Smoothing red part of the lip (ml)	Bitterness folds	Breasts	Scar	Follow up (month)
Pat.1 M.V	F				2 x 0.6 (16.09- 22.10)					3
Pat.2 I.C.	F		0.6							2
Pat.3 M.N.	F	0.15	0.3							3
Pat.4 S.E.	F			2 x 0.3 (30.09- 03.11)						3
Pat.5 G.A.	F				0.3 insuf.					2
Pat.6 V.M.	F							0.4	0.2	now in U.S.A.
Pat.7 M.P*	M				0.1		0.5			2
Pat.8 H.L.A.	F		0.2							2
Pat.9 G.J	F	0.2	0.2							1
Pat.10 R.S.	F		0.6							2
Pat.11 E.T*	F		0.25		0.4					

** Allergic patients (biopsies + positive antibodies) to - Restylane - Hylaform® (3).*

4.2 Contra-indications and precautions for use

We show in table 1, the data proposed both in conferences and university courses, in which we have taken part, or the leaflets from the manufacturing companies.

5. CONCLUSIONS

We have had the privilege of experimenting on an injectable hyaluronic acid for aesthetic use to fill wrinkles. This has a specific design giving it a cohesive polydensified matrix. This cross-linking technique allows a filling effect to be obtained which should last for 9 to 12 months with a maximum of 2 injections separated by 2 1/2 to 3 months (photo 5).

Photo 5: Esthélis® Max. Result after 6 month.

Past history of auto-immune disease	Patient	Family
Active rheumatoid arthritis		
Psoriatic arthropathy		
Ulcerative colitis (U.C.)		
Crohn's Disease (non auto-immune inflammatory disease)		
Lupus-erythematosus		
Polyarteritis nodosa		
Sclerioderma		
(Dermato) Polymyositis		
Sjögren's Syndrome		
Basedow Disease (Thyroid)		
De Quervain Disease (Thyroid)		
Hashimoto's thyroiditis		
Fleisinger Leroy Weiter's Syndrome		
Alopecia (hair destroying)		
Raynaud's Syndrome		
Ankylosing spondylitis		

Esthélis®, hyaluronic acid of Swiss design. First complete study of the physico-chemical characteristics and clinical trials.

The secondary effects seen in this 1st study were minimal and we would state in particular that to date patients who have developed an allergic reaction to biphasic hyaluronic acids have been able to be treated without any secondary reaction, after of course performing a double intradermal allergy safety screening test.
Esthélis® could therefore be the bioferementation origin resorbable filling substance which we are looking for, which perhaps only requires 1 maintenance treatment per year once the first 2 sessions have been performed.

Past history of allergy	Past	Present
Atopic dermatitis		
Asthma		
Pollen induced rhinitis		
Chronic urticaria		
Quincke's oedema		
Egg proteins (ovomucoid (Hylaform))		
Chicken proteins (hyaluron)		
Local anaesthesia (lidocaine)		
Collagen allergy		

Diseases	Yes	No
Epilepsy		
Cutaneous porphyria		
Vitiligo		
Psoriasis		
Seborrhoeic dermatitis		
Herpes (fever spot)		
Repeated sore throats		
Cheloid scars		

In childhood	Yes	No
Acute rheumatic fever		
Osler Rendu endocarditis		

Immunosuppressant treatments, chemotherapy, HIV, pregnancy and lactation

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We wish to express our most sincere thanks to Dr. Didier Sarrasin from Laboratoire Weintraub, Geneva for his valuable assistance and continuous availability for our work and for his generous contribution to the work.

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Dermal filler under histopathologic examination[1]

Test design

- Objective: Observation of histological local reactions after implantation of absorbable filling material
- Test persons: Female patients with planned abdominal adipositas surgery, age: 44-69 years
- Material: Absorbable hyaluronic acid fillers: Belotero®, Juvederm®, Restylane®, Teosyal®
- Method: Intradermal implantation of the dermal fillers in marked skin areas dextral and sinistral of the center point of the volume

  0.2 ml per dermal filler using the same injection technique at the same distance from one to the other

  Biopsy after 14 days: from the left side
  Biopsy after 30 days: from the right side

Criteria for the evaluation of local tissue reactions

- Marks for inflammation/foreign body reaction

Lymphocytes (L) | Plasma Cells (P) | Eosinophil Granulocytes (EG)

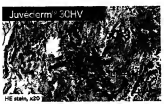
[1] Seckig A, Sattler A, Kühnel W (2009)
Neue Strategie zur Erfassung intradermaler Reaktionen nach Implantation resorbierbarer Dermalfiller.
J Ästhet Chir 2009;2: 29 - 36 © Springer Medical Publishing 2009
(Abstract also available in English)

BELOTERO®

Belotero® Intense: Free of foreign body reactions

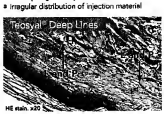
Biopsies after 30 days p.i.

- No histomorphological inflammation reaction
- Even distribution of injection material



- Light to moderate chronic inflammation
- Increased lymphocytes, plasma cells, and eosinophil granulocytes
- Irregular distribution of injection material

- Intense chronic inflammation
- Heavy infiltration of lymphocytes, plasma cells, and eosinophil granulocytes
- Irregular distribution of injection material



- Intense chronic inflammation
- Irregular infiltration of lymphocytes and plasma cells

Belotero® is the only dermal filler in this study showing an even distribution of the material as well as an excellent compatibility tolerance

- No abnormality with Belotero®
- No noteworthy local inflammation reactions

Belotero® Intense: A high level of safety for physician and patient

HE = hematoxylin and eosin
x20 = magnified by a factor of 20

BELOTERO®

REVIEW ARTICLE

www.jcasonline.com

Soft Tissue Augmentation in Dermatology – 2009 Update

The number of products available to dermatologists for soft tissue augmentation has grown significantly over the past several years in the US. This manuscript will review the various hyaluronic acid fillers and other Food and Drug Administration -approved products we are utilizing for our patients in the rejuvenation process. It is hoped that through this article clinicians will feel more comfortable using these products in their everyday practice of dermatology.

KEYWORDS: Dermal filler, non-invasive, hyaluronic acid, soft tissue augmentation

INTRODUCTION

The field of soft tissue augmentation has had a rapid growth over the past several years, mainly due to the development of the hyaluronic acid (HA) fillers and other fillers now routinely utilized for rejuvenation of the skin. These products have changed the paradigm for clinicians as we search for new ways to treat the ageing face, especially as we treat facial lines, wrinkles, and volume loss, commonly associated with facial ageing.

Over the past several years, there has been a dramatic rise in the number of 'non-invasive' cosmetic procedures being performed by clinicians. This trend started with the release of botulinum A toxin (Botox™), and according to the 2008 statistics from the American Society for Aesthetic Plastic Surgery (ASAPS), the injection of Botox™ continues to lead in the number of procedures being performed. It has been reported that the injection of Botox™ is the number one cosmetic procedure being performed in the world at this time. Next in line to Botox™ injections is laser hair removal, which is the second-most common noninvasive cosmetic procedure, followed closely by the injection of HA fillers, which has steadily 'climbed' up the ladder over the past several years. In 2008, ASAPS reported that their members utilized HA fillers in 1,262,848 procedures.[1] This trend is mirrored by other reporting organisations, including the American Society for Dermatologic Surgery (ASDS). Other fillers, not often included in these surveys, make these numbers even higher.

IDEAL DERMAL FILLER

Clinicians have been wrestling with this concept for many years and we may just be approaching this 'ideal' group of products with the HA fillers and some of the other fillers now available. The fillers should be easy to inject, produce reproducible results and have a longevity profile that is satisfactory to both the patient and the physician. When we speak of longevity, most would agree that for a filler to be effective, it should last for a period of at least one year or perhaps as long as two years. Clinicians also want an ideal filler to be painless upon injection, to be non-allergenic, which means no skin testing prior to injection, non-carcinogenic, non-teratogenic, and one which, when injected, shows little migration over time. The ideal filler must have a long 'shelf life' and be free from all transmissible diseases. It must also have few, if any, untoward effects following the injection into the skin. Cost is also a factor for the ideal filler; the filler must be affordable to both the physician and the patient receiving it.[2]

CLASSIFICATION

Fillers have been classified by many over the years, and it is beyond the scope of this manuscript to get into debates and discussions on the various classifications with regard to which group of fillers in these classification systems is better than the other. What is important for the discussion at hand is that there are fillers that

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can be classified as non-permanent and those that are considered permanent.[3] Non-permanent fillers are the most popular at this time and we continue to see an increase in their use and in the number of these fillers reaching the market. These fillers usually last upto one to two years for some products. Permanent fillers may have a role for certain patients and in the hands of skilled injectors.

In this manuscript, we will focus first on the HA fillers, a group of products which, as noted, has changed the face of soft tissue augmentation. We will also review the other Food and Drug Administration (FDA)-approved products for soft tissue augmentation, and highlight some of the current research initiatives going on in this most exciting cosmetic field.

HA fillers, as noted, is the largest group of non-permanent fillers available for soft tissue augmentation. These include Restylane® and Perlane®, Juvederm® Ultra and Juvederm® Ultra Plus, Elevess (now known commercially as Hydrelle™), and Prevelle® Silk. The newest of the collagen fillers, Evolence®, also available in the US, will be discussed, as well as, some of the semi-permanent fillers, known commercially as Radiesse® and Sculptra®. The one permanent filler available in the US, known as ArteFill®, will also be described here.

DIFFERENT FILLERS AND THEIR CHARACTERISTICS

In the US, the bovine collagen products, known as Zyderm® and Zyplast®, were the first to be introduced to dermatologists, in the field of soft tissue augmentation in the early 1980s. It became the standard for many years and many patients experienced very impressive cosmetic enhancements as a result of the collagens. They required skin testing, and many recommended double skin testing to minimize the potential for allergy to the bovine collagen. For almost 20 years, this along with human-derived CosmoDerm® and CosmoPlast® were all we had; and then the doors or floodgates opened, thanks to new fillers making their way through the FDA and into the hands of dermatologists, for the benefit of our patients.[2]

Hyaluronic acid fillers

In order to understand HA fillers, some basic terms and characteristics that make HA fillers unique, are needed. HA or hyaluronan is a glycosaminoglycan, which consists of repeating non-sulphated disaccharide units of glucuronic acid and N-acetylglucosamine.[4] HA, a naturally occurring substance, is a biopolymer and it exhibits no species or tissue specificity. HA is an essential and abundant component of the extracellular matrix in all animal tissues. HA is highly hydrophilic and therefore attracts water, and helps form large concentrations that can occupy a large volume relative to its mass. It has been found to form gels at even low concentrations. When water is drawn into the HA matrix, it creates a swelling pressure or turgor that enables the HA complex to withstand compressive forces. These characteristics and in particular, the fact that HAs do not exhibit tissue or species specificity, which plays a crucial role in minimizing any potential immunological reactions or other allergic potentials have helped make HA fillers popular among clinicians injecting patients, to improve fine lines and wrinkles and for volume enhancement.

The first HA developed as a dermal filler dates back to 1989, when Balazs *et al.* described the first injectable HA filler.[5] Although it was not a long-lasting dermal filler, the HA 'revolution' had begun.

Factors which are important in characterizing a HA filler

Several differentiators have become important in their development. These include: the source of HA, the concentration of HA being utilized, the particulate size of the HA, the cross-linking of HA and the type of cross-linking agent being used, whether the HA is monophasic or biphasic, and whether an anaesthetic is added to the syringe or not. Some of the original HA fillers used avian rooster combs as the source for their HAs, but more commonly the source is bacteria-based, mainly from the fermentation of the *Streptococcus equine* bacterium. Most of the newer HA fillers have higher concentrations of HA compared to the older materials. It is felt that those HA fillers with higher concentrations of HA may be longer lasting, therefore, those with concentrations of greater than 20 mg/ml are considered ideal for HA fillers at this time. Cross-linking is important and most utilize ether cross-link bonds to help stabilize the HA. The newer non-particulate HA fillers contain double cross-linking, multiple cross-linking bonds. They may be also in monophasic gels, in an attempt to stabilize the molecule even more. This cross-linking makes the HAs less resistant to degradation, and thus enhancing longevity. As a result of the cross-linking process and non-particulate nature of newer HAs, higher HA concentrations are required to prevent biodegradation from free radicals and other enzymes. This leads to enhanced longevity of the filler. 1, 4-butandiol diglycidylether (BDDA) and 1, 2, 7, 8-diepoxyoctane are the commonly used cross linking agents. Larger HA particles tend to last longer as fillers, and are usually designed for deeper filler injections.

Both monophasic and biphasic fillers have their advantages; monophasic HA fillers are more cohesive, may last longer and may not migrate as much following its injection. However, biphasic HA fillers are more easily customized, to obtain the appropriate particle

size to suit the indication and the anatomic area being treated.[2]

Numerous HA fillers are available in Europe and elsewhere around the world. In the US, due to a more stringent FDA approval process, there are fewer products available; although recently, many more are undergoing clinical evaluation through FDA-approved protocols. The remainder of this manuscript is going to focus on the fillers available in the US, reviewing their clinical studies and FDA approvals.

Analysis of results of different fillers

a) Restylane family: The first of the 'new' fillers in the US was Restylane. Restylane received its FDA approval in the US in December 2003, although it received its EU clearance much earlier, in 1996. It has been injected in well over ten million treatment sessions worldwide and is considered the standard against which all other and all new HAs are measured. It is manufactured by Q-Med AB (Uppsala, Sweden) and is marketed in the US and Canada by Medicis Pharmaceutical Corporation (Scottsdale, AZ USA). Restylane is a non-animal stabilized HA, commonly referred to as NASHA, produced from the fermentation of equine streptococci. It is cross-linked with BDDA, with a 1% degree of cross-linking. Restylane has an HA concentration of 20 mg/ml and its gel particulate size is 400 μm. It has a particulate size of 100,000 gel particles per milliliter and is the first of the Restylane family of products available from Q-Med and Medicis. Restylane's FDA approval is for mid-dermal applications, such as, deep wrinkle correction, lip augmentation, nasolabial fold correction and for glabellar creases. It received its initial FDA approval for six months duration of correction. Restylane has also been successfully used in the treatment of tear trough deformities
Perlane, the second product released in the Restylane family, contains 8000 gel particles per milliliter and is indicated for deeper injections and deeper clinical defects. In other parts of the world, this product is known as Restylane Perlane.[6]
Other products in the Restylane family include Restylane Touch™, Restylane Lipp™, Restylane SubQ™ and Restylane Vital™. A newer product, known as Macrolane™, has been introduced into Europe, mainly designed for volume enhancement. Further information on these products can be obtained from Restylane website.[7]
The two pivotal European clinical trials that led to the approval of Restylane in Europe will be discussed in detail here. These trials, by Duranti *et al.*[8] and Olenius[9] showed the safety and efficacy of Restylane in the correction of the nasolabial folds. In the first trial by Duranti *et al.*, 78% of the patients who enrolled found that they were able to maintain moderate-to-marked clinical improvement for eight months following the injection. In the second study, by Olenius, there was correction of 82%, noted at 12 weeks and 69% at 26 weeks. Adverse events (AEs) noted in these two clinical trials were predominantly injection-related AEs, consisting of treatment-site erythema, hyperpigmentation at the treatment site and pain from the injection itself, reported in 13% of the patients in these trials. As experience grew with the product, injection techniques were refined, a later study of a large series of patients, Friedman *et al.*,[10] found that the injection related AE rate was, in fact, occurring in only 0.15% of the patients receiving Restylane injections.
Shortly after these reports, several cases of what was described as delayed implant hypersensitivity, were reported in European literature.[11-13] Through these evaluations, it was determined that there was a 0.4 to 3.7% risk of this occurring following Restylane implantation. As a result of this delayed implant hypersensitivity occurring in more patients than was acceptable, a more purified Restylane product was manufactured by Q-Med, and this more purified product, NASHA, is what is currently available today. Clinical evaluations with the new purified Restylane and with clinicians mastering their injection technique, AEs were reduced to 0.06% and hypersensitivity reactions were reduced to 0.02%, and threrfore considered acceptable for continued use. This helped in the acceptance of this new NASHA product on a broader basis. These factors, and the fact that HAs in general requiring no skin testing prior to injection as stated earlier, led to the commencement of the pivotal US clinical trials for Restylane.
The US clinical trials for Restylane compared Restylane in one nasolabial fold with Zyplast collagen, the standard collagen injectable material available at that time, being injected into the other nasolabial fold. In this clinical trial by Narins *et al.*,[14] 138 individuals were included for evaluation. The majority of the patients enrolled were females (93%) and Caucasians (89%). The protocol design consisted of injection in each nasolabial fold with each product for optimal correction. The patients were asked to return at two weeks for any touch-up injections if needed. Optimal correction was the goal of the injection process and patients were allowed two sessions if needed, to achieve their optimal correction. The study results showed that optimal correction was achieved in 1.4 sessions for both the products being injected. The volume needed for Restylane, for volume correction, showed a mean

of 1.0 ml (range 0.3 to 2.8 ml), while the amount of Zyplast used showed a mean of 1.6 ml (range of 0.1 to 5.0 ml). The Wrinkle Severity Rating Scale (WSRS) score for Restylane was superior at all time points, as compared to the Zyplast side. This was true at two months, four months, and six months following the optimal correction of the nasolabial folds. At the six-month evaluation Restylane was rated superior in 56.9% of the patients compared to Zyplast in 9.5% of the patients. The Global Aesthetic Improvement Scale (GAIS) was also superior for Restylane at all time points, with a 62% rating for Restylane superior at six months, as compared to 8% rating for Zyplast superior.

Adverse events were evaluated at each follow-up visit during the course of the study. Mild-to-moderate injection site reactions occurred in a similar and non-statistical fashion with both the products (93.5% Restylane, 90.6% Zyplast). These were short-lasting in all cases, usually resolving within seven days. Of all treatment-related AEs during the evaluation, 26.4% were reported for Restylane and 39.1% for Zyplast. Delayed-onset reactions were noted in 8.7%; all resolved within two to three months without intervention. There were no reports of hypersensitivity reactions reported during the trial.

Further evaluations have been performed with Restylane over the past several years in the US.[15-17] The evaluations have continued to show the safety and efficacy of this product in each and every study. Two of the US clinical evaluations are very important and warrant in depth discussion. The first, by Odunze *et al.*,[18] evaluated 60 patients who received Restylane injections, one-third of whom were of darker skin types, (Fitzpatrick skin types IV - VI). They noted no untoward AEs in the darker skin color group, providing evidence that Restylane can be safely injected into patients of all skin types. The second study, by Narins *et al.*,[19] also studied Restylane, but looked at repeat injections and longevity associated with repeat injections in seventy-five patients in a multicenter evaluation. The patients were randomized to receive retreatment of one of their nasolabial folds at 4.5 months and the contralateral fold at nine months after correction of both folds at the initial visit. Results were presented and analyzed at 18 months. The WSRS improved significantly ($p < 0.001$) from baseline, with mean improvement noted from 1.1 to 1.7 grades. Ninety-seven percent of all the patients responded to this retreatment program, and the efficacy of the retreatment schedules did not differ significantly. The AEs reported were all local and consisted of swelling and bruising at the treatment site, which occurred in 33%, and were not rated as serious in this study. Thus, Restylane was shown to maintain correction for 18 months following a repeat injection at 4.5 months. This study led to a second submission to the FDA, known as a supplemental PDA, for its label, giving a new indication for Restylane longevity up to 18 months with a repeat injection at 4.5 months.

Following the approval of Restylane, Perlane received its FDA approval for deeper dermal defects, especially for those have deep nasolabial folds and for other lines and wrinkles that require a larger particle size HA filler. Lastly, clinical studies are at the concluding stage at this time, on a new Restylane product with lidocaine incorporated into the syringe itself. More information on this product should be available soon. Clinical examples of Restylane are shown in Figures 1 and 2.

b) Juvederm family: The next group of HA is known collectively as Juvederm. Juvederm is manufactured by Lea Derm, a subsidiary of the Corneal Group (Paris, France). It was brought to the US by Inamed and was purchased several years ago by Allergan, Inc. Allergan, the makers of Botox™, are the current distribution source worldwide for Juvederm. There are two current formulations of Juvederm available in the US – Juvederm Ultra and Juvederm Ultra Plus. Six different formulations of Juvederm have been developed by Corneal, with differing concentrations of HA in each formulation, ranging from 18 mg/ml to 30 mg/ml. Both the available US products contain 24 mg/ml of HA, respectively, with Juvederm Ultra Plus containing 24 mg/ml of HA in high viscosity. Both the US Juvederm formulations were FDA approved in June 2006 – Juvederm Ultra for deep wrinkles and defects and Juvederm Ultra Plus for deeper furrows, such as, the nasolabial folds. The Juvederm family is produced from the bacterial fermentation of equine streptococci. The HA is cross-linked with a patented single-phase BDDE-phosphate buffered from 6.5 - 7.3 pH. With a higher concentration of HA and more cross-linking than other HA fillers, it has been suggested that the Juvederm family of products may persist longer than other HA fillers, and also have a smoother injection flow.[20]

Baumann L *et al.*,[21] , in an important clinical trial, compared three Juvederm products, with Zyplast collagen, in the treatment of nasolabial folds. Four hundred and twenty-three patients completed the clinical trial of a 24-week evaluation. Over 300 patients received an additional treatment, at the conclusion of the clinical trial in order to further examine the long-term efficacies of these products. Results from this multicenter clinical evaluation showed that both, the Juvederm family, and the Zyplast collagen, showed significant improvements

at all points during the course of the 24 week clinical trial. The three products of the Juvederm family studied showed a significantly greater efficacy than the bovine collagen product; the efficacy increased with time and was greatest at 24 weeks after the last treatment. Utilizing a four-point scale, an improvement of at least one point was seen in more than 80% of the Juvederm-treated patients compared to a 0.5 improvement, on an average, in the Zyplast-treated patients. At the end of 24 weeks of injection, long-term results showed that there was 57% improvement at eight months, 37% at 10 months, and 18% at 12 months.

Adverse events were similar for both the Juvederm side and the Zyplast side that were treated, and were similar for all of the Juvederm products studied. Mild-to-moderate treatment site reactions were seen in a majority of patients, all of which resolved within seven days. No long-term adverse reactions were noted. Patient preference data suggested a 78% preference for Juvederm 30, 88% for Juvederm 24HV, and 84% for Juvederm 30HV. From this clinical study, Juvederm 24HV and Juvederm 30HV were chosen for the US market, both of which contained 24 mg/ml of HA, with Juvederm Ultra having 9% cross-linking, while Juvederm Ultra Plus had 11% cross-linking. Because of the long term follow-up during this multi-center clinical trial, the investigators were able to show longevity at one year following optimal correction, and therefore, were able to receive FDA clearance for up to one year.[22]

Most clinicians who utilize Juvederm have noted that it does inject easily through the syringe and that results are commonly observed for 6 to 12 months. Local injection site reactions are rare and there has been some discussion that the injection of Juvederm results in a more natural appearance than the other HA fillers, although no clinical studies with regard to this debate have been performed. Clinical examples of Juvederm are seen in Figures 3 and 4. A newer form of Juvederm, with lidocaine incorporated into the syringe itself, is now available in Europe, and pending FDA approval in the US at present

c) Hydrelle: The next HA filler that received FDA approval was originally known as Elevess and is currently known as Hydrelle. Hydrelle is marketed through Coapt Systems (Palo Alto, CA, USA) and is manufactured by Anika Therapeutics (Bedford, MA, USA). Hydrelle contains the highest concentration of HA of all products, in the market at this time, 28 mg/ml, and it also contains 0.3% lidocaine, the first of the US products receiving FDA clearance for an HA with lidocaine. It is cross-linked with p-phenylene bisethyl carbodiimide or biscarbodiimide or BCDI, which is a novel HA cross-linker. Its source of HA is from equine streptococci. The US clinical pivotal study for Hydrelle (Elevess) studied 191 individuals who received Elevess in one nasolabial fold and CosmoPlast in the other nasolabial fold. Patients had significant improvement in the Elevess side at both four and six months following optimal correction. AEs were similar in both groups and not significant. They consisted mainly of treatment site reactions and resolved in the majority of cases within seven days.[23] Patients who still had improvement at the six-month time frame were eligible to enter a nine- (n = 90) and 12 month (n = 84)

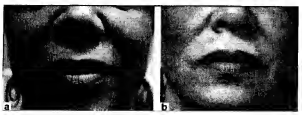

Figure 1: Before treatment (a) and after treatment with Restylane (1.0 cc) to nasolabial folds (b)

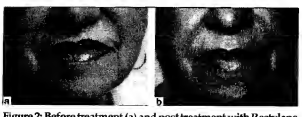

Figure 2: Before treatment (a) and post treatment with Restylane (1.0 cc) to the nasolabial folds and marionettes lines (b)

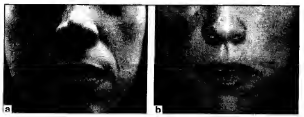

Figure 3: Before treatment (a) and immediately post treatment with Juvederm (1.0 cc) to the nasolabial folds and tear trough (b)

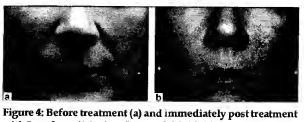

Figure 4: Before treatment (a) and immediately post treatment with Juvederm (1.0 cc) to the nasolabial folds and marionettes lines (b)

extension follow-up clinical trial. The patients maintained their improvement at these time frames as well; with the Elevess side showing more improvement than the CosmoPlast side.[24]

In clinical practice, this material is easy to inject with a 27 gauge needle; however, the 30 gauge needle supplied with the syringe makes the injection process a little more difficult than most of the other HA fillers. The addition of lidocaine is a benefit and most patients note a decrease in pain, almost immediately after the first injection into the skin.

d) Prevelle: The next HA filler that received FDA approval is known as Prevelle™ Silk. This product is the next generation of an earlier HA filler, known as Captique™, which is not available anymore. Captique was manufactured by the Genzyme Corporation (Cambridge, MA, USA) and was originally marketed by Inamed and then Allergan, and was later sold to the Mentor Corporation (Santa Barbara, CA, USA), who now markets the newer formulation of Captique, known as Prevelle Silk. more recently, Mentor HAS BEEN purchased by Johnson (Skillman, NJ USA). The product contains 4.5 – 6.0 mg/ml of HA, is 20% cross-linked with divinyl sulphone and has a gel particle size of 500 μm. On account of the low concentration of HA in the product, the clinical results were of short duration, in the three to six month time period. Prevelle Silk combines Captique with 0.3% lidocaine and the pivotal trials for this product, conducted by Monheit *et al.*,[25] showed that Prevelle Silk had a significant difference in pain associated with the injection process and postprocedure pain. The majority of patients receiving Prevelle Silk do not have significant post-treatment erythema or post-treatment swelling. Patient preference was also significantly more in favor of the Prevelle Silk over Captique. Prevelle Silk is generally preferred for patients needing instant correction with very little potential for adverse effects. Genzyme and Mentor have more fillers on the horizon, which will be part of the Prevelle family. The first of these products should be available towards the end of 2009 or early 2010.

PRODUCTS USED FOR SOFT TISSUE AUGMENTATION

a) Collagen: Is there still a role for a collagen product to be useful in today's world for soft tissue augmentation? The answer is definitely yes. A new 'porcine' collagen has become available for use in the US recently and is gaining market share, as dermatologists become more attuned to its injection techniques and its longevity once implanted. It is known commercially as Evolence and is manufactured by ColBar LifeScience Ltd. (Hertzelia, Israel), which is now part of Johnson and Johnson (OrthoNeutrogena Aesthetics, Skillman, NJ, USA). Evolence utilizes a specialized process of stabilization known as 'glymatrix,' in which there is ploymerization of the monomeric porcine collagen by glycation with ribose, a naturally occurring sugar. This glymatrix technology helps the porcine collagen form a three-dimensional gel network, which helps create a more stable, longer lasting filling material. The porcine source is from a closed herd in Australia and the glymatrix process takes place in Israel. Evolence received its FDA clearance in June 2008.

Clinical studies with Evolence have shown its effectiveness. Skin testing data by Shoshani *et al.*,[26] have demonstrated that there is virtually no immunogenicity to this product. Five hundred and thirty patients were evaluated for hypersensitivity reactions to Evolence and none were found in this clinical trial. Thus, skin testing for Evolence is not required. The first EU study on Evolence[27] evaluated Evolence in one nasolabial fold and Zyplast in the other nasolabial fold. None of the patients demonstrated skin test reactions and longevity of the Evolence was maintained upwards of 18 months following implantation. The US pivotal study by Narins *et al.*,[28] evaluated Evolence in one nasolabial fold and NASHA in the other nasolabial fold. A total of 149 patients were enrolled in this multicenter clinical trial. There were significant improvements noted in both nasolabial folds at six months (non-inferiority study), with more AEs noted on the NASHA side as compared to the Evolence side. An extension study for evaluation of patients receiving Evolence at 12 months was also performed and did show significant improvement in 12 months. The FDA approved a 12 month labelling for Evolence in June 2009. Further evaluations in a multicenter evaluation with Evolence continue at this time, especially in patients with coloured skin, with results expected to be available by the end of 2009.

A second Evolence, known as Evolence Breeze, is indicated for more superficial lines, wrinkles and lips. This product is available in many countries around the world; US clinical trials are supposed to start shortly. This implant requires a more sophisticated injection technique than that of the typical HA filler. On account of its unique nature and processing, Evolence needs approximately one hour to 'set in'. Therefore, massaging immediately after the injection itself allows for proper moulding of the implant, which will then be in place for the duration of the implant. Some

patients continue to feel the effect of the injection at the treatment site for several days to weeks after being injected with Evolence, but this resolves and patients enjoy this implant for many months. In fact, most patients note that this product lasts for 12 to 18 months. Clinical examples of Evolence are shown in Figures 5 and 6.

b) Radiesse: Radiesse, a semipermanent filler also known as calcium hydroxylapetite (CaHA), contains synthetic CaHA microspheres (30%) suspended in a carboxy-methylcellulose resorbable aqueous gel carrier (70%). This process allows for the body's stimulation of collagen. Skin testing is not required for Radiesse injections. Radiesse was approved by the FDA in December 2006, and is indicated for the treatment of facial wrinkles and folds, as well as, the correction of facial wasting as a result of HIV-associated lipoatrophy. It was the first filler to receive these two FDA indications. Pivotal US clinical trials for both these indications showed significant improvements[29,30] and many studies have demonstrated longevity with Radiesse, for over one year and up to two years.[31-33]

Radiesse has found a niche role, with many clinicians who are looking for a more 'robust' filler and long-lasting results. It also has become one of the favourite fillers for hand rejuvenation, utilizing injections of Radiesse into the dorsum of the hands and then massaging to mould the Radiesse into the skin. Many clinicians have also incorporated lidocaine into the Radiesse syringe through an adaptor process – this has recently received FDA approval as it has become the standard of care.

c) Sculptra: Sculptra, or poly-L-lactic acid, another semipermanent filler, has been available in the US market for the past several years with FDA approval in 2004, to treat HIV-associated lipoatrophy. In July 2009, Sculptra received FDA clearance from the FDA to treat lines and wrinkles for aesthetic considerations. It is best used as a volume enhancement treatment and requires several treatment sessions to achieve the desired effect. The early Sculptra studies in Europe[34,35] showed the efficacy of this product. The first of these, known as the VEGA study[34], evaluated 50 individuals and found an increase in skin thickness, which was significant, in all the studies conducted at various times. The material was found to be persistent after a full correction for upwards of two years. Visual improvements, confirmed by serial photographic analysis, confirmed the results. The second European study[35], known as the Chelsea and Westminster Study, evaluated 29 patients. Once again, an increase in skin thickness was found in all the patients studied. There was a mean change of 4 to 6 mm noted at 12 weeks following correction.

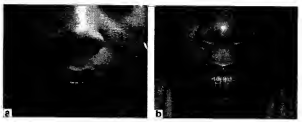

Figure 5: Before treatment (a) and after treatment with Evolence (1.0 cc) to left nasolabial fold (b)

Figure 6: Before treatment (a) and after treatment with Evolence (1.0 cc) to marionette lines, upper lip, vertical lines (b)

Also, improvements in anxiety and depression scores were noted in these subjects, as a result of increased self-esteem due to this therapy.

In the US, two pivotal FDA clinical trials were performed in HIV-associated lipoatrophy patients. They are known as the APEX002 (n = 95) and the Blue Pacific (n = 68) studies.[36,37] Both these studies showed the effectiveness of Sculptra in HIV-associated lipoatrophy.[36,37] Many other, recent studies confirm these original trials and the effectiveness of Sculptra for several years duration.[38,39]

As noted, for Sculptra to achieve its full correction, the patients need a series of injections. The injections are usually spaced four to six weeks apart. It is important to inform the patients with HIV-lipoatrophy about this fact- that two to four injection sessions may be required for the poly-L-lactic acid to stimulate new collagen and reverse the signs of lipoatrophy. However, for cosmetic enhancement, one to three sessions are usually sufficient. There are also various techniques to prepare the product for the injection and each clinician will develop his/her 'favorite' technique. The authors usually mix 5 cc of sterile water with 1 cc of 0.3% lidocaine and let the medicine set for 24 hours prior to the injection of the Sculptra. Most of the experience with Sculptra, in the US, has been with patients suffering from HIV associated lipoatrophy and there is no doubt that the product has changed their lives for the better.

d) Artefill: The last filler that is being discussed in this article is a permanent filler, known as ArteFill, being promoted by Suneva Medical Inc. (San

Diego, CA, USA). This is an interesting filler, composed of polymethyl-methacrylate (PMMA) microspheres suspended in a rapidly dissolving bovine collagen carrier, with 0.3% lidocaine added to the syringe. It was designed in this fashion to induce 'reactive' long-term collagen deposition. The PMMA microspheres are from 30 to 50 μm in size, too big to be phagocytised within the body, but small enough to be easily injected through a 26 gauge needle. This product has had several previous lives, first as ArtePlast, and then ArteColl, and now ArteFill. The previous generation products differ from today's products in many ways and it is sufficient to say the current product is safe and effective. ArteFill received FDA approval in October, 2006. In the US pivotal clinical trial, ArteFill was compared to Zyplast or Zyderm collagen in the nasolabial folds.[40] Two hundred and fifty-one patients were enrolled in this trial and at six months, the collagen sides were crossed-over to receive ArteFill also. Furthermore, at six months, a significant change was noted in the nasolabial folds which received ArteFill, while the collagen sides had returned to their baseline. AEs were similar between both the groups.[40] Safety studies for ArteFill continued successfully for 12 months. Since the US pivotal clinical trial, there is an ongoing five-year safety trial for ArteFill, which is currently in year three. The purpose of this study is to examine the long-term effects of ArteFill, including its efficacy as well as its safety.

While ArteFill has had a checkered history in the US market, it is a very good filler for patients with deep dermal defects, who understand that the filler being placed will last anywhere from one to five years, depending on numerous factors, including the level of skill of the injector and the proper placement of the product.

SUMMARY

Soft tissue augmentation remains a growing field. There are very good fillers currently available and many more on their way. We, as dermatologists, have an array of treatment options available to help rejuvenate the skin of our patients, and dermal fillers are part of that process, along with botulinum toxin A, lasers and light sources and appropriate skin care. Combining different modalities will yield the best results.

It is often hard to study and be familiar with 'all' the fillers. It is appropriate to understand one or two and use them well. One should be aware of what makes each filler unique and where each filler might have its optimal place for injection. Learning proper injection techniques is important and learning from your peers is an opportunity that will allow you to acquire the skills you need to make you the best injector possible.

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